Type 2 diabetes, its pharmacological treatment and associations with cancer

Overbeek, J.A.

2019

document version
Publisher's PDF, also known as Version of record

CHAPTER 1

General introduction, outline and data sources

INDEX

Diabetes

Diabetes mellitus, commonly referred to as diabetes, is one of the largest global health emergencies of the 21st century.[1] It is associated with high disability and premature mortality and symptoms of this chronic metabolic disease include increased urination and excessive thirst and hunger. Furthermore, diabetes is characterised by hyperglycaemia (i.e. elevated blood glucose levels) which is associated with both micro- (neuropathy, retinopathy, nephropathy) and macrovascular complications (coronary artery disease, cerebrovascular disease),[2, 3] which have a substantial negative influence on a person's quality of life.

Worldwide, the prevalence of diabetes in 2015 is estimated at 415 million.[1] Despite better awareness and new developments in treatment of diabetes and prevention of type 2 diabetes (T2D), the number of persons with diabetes increases. In most countries, this increase was alongside cultural and social changes: ageing populations, increasing urbanisation, reduced physical activity and increased overweightness. In the Netherlands, more than 1.1 million persons had diabetes (69.7 per 1,000 men and 62.9 per 1,000 women) in 2017.[4]

Type 1 diabetes (T1D) and T2D are the major forms of diabetes, T1D accounts for 5-10% of all diabetes cases and T2D for 90-95%. In T2D, there is a relative insulin deficiency resulting from a progressive insulin secretory defect on the background of insulin resistance. Genetic and environmental factors, such as excess body weight and lack of physical activity seem to contribute to onset of the disease. The current thesis mainly focuses on T2D.

In the Netherlands, T2D is mainly treated by general practitioners (GPs). Treatment usually starts with lifestyle management by smoking cessation, increase in physical activity, weight control and a healthy diet to decrease hyperglycaemia. As the disease progresses, pharmaceutical treatment is usually required. Since 2006, the Dutch diabetes guideline for GPs, issued by the Dutch College of GPs (NHG guideline T2D)[5] recommends a step-wise approach with metformin as the first drug. Addition of a sulfonylurea (SU) derivative is recommended if glycaemic control is not achieved. If persons do not reach the HbA_{1c} target with this combination, insulin should be added. Since July 2018, this step-wise approach was updated and instead of adding insulin to the combination of metformin and SU, there is now also room for the addition of a newer incretin-based therapy (i.e. dipeptidyl-peptidase-4 [DPP-4] inhibitors and glucagon-like peptide-1 [GLP-1] receptor agonists).[6] The aim of the guideline is to prevent or delay the occurrence of micro- and macrovascular complications.

Cancer

Cancer is a group of diseases that are referred to as malignant neoplasms. Malignant neoplasms are characterised by abnormal cell growth and division and have the potential

to invade or spread to other parts of the body. In the Netherlands, the 10-year prevalence of cancer almost doubled from 1.8% in 1999 to 3.3% in 2016 and is expected to increase further.[7] In 2016, the most occurring cancer types were prostate, colon and skin (excluding basal cell carcinoma) cancer among men and breast, skin (excluding basal cell carcinoma) and colon cancer among women.[8]

Association between type 2 diabetes and cancer

Because of the increased prevalence of both diabetes and cancer, it is likely that these diseases also occur together more often within the same individual. In the Netherlands, the number of people with both diabetes and cancer doubled in the past 15 years.[9] Epidemiological studies suggest that people with diabetes are at significantly higher risk for many forms of cancer. Meta-analyses of cohort studies[10-16] show increased risks of cancer ranging from 1.25 for breast cancer to 2.23 for hepatocellular carcinoma. On the contrary, in men with T2D a decreased risk of prostate cancer is observed (RR = 0.84; 95% CI: 0.76-0.93).[17]

Several mechanisms have been proposed for the increased risk of cancer among people with T2D, such as common risk factors, the specific metabolic derangements of diabetes itself (i.e. hyperglycaemia, hyperinsulinemia and insulin resistance) and the use of glucose lowering drugs.

Common risk factors

It has been published that diabetes and cancer have several risk factors in common, such as older age, obesity, lack of physical activity and poor diet. Increasing age is associated with diabetes, because of bodily resistance to insulin due to increased adiposity, decreased lean muscle mass, changes in dietary habits, and reduced physical activity.[18] Furthermore, the pancreas starts to produce insulin less effectively as age increases.[19] For cancer, advancing age is the most important risk factor. Older individuals might be more susceptible to oncogenic mutations or cells might need time to accumulate enough mutations to become cancerous.[20] Obesity, mainly due to anthropometric parameters and lifestyle factors, activates different biological mechanisms (e.g. hyperinsulinemia, insulin resistance, vascular growth factors, oxidative stress, and alterations in immune function), resulting in a higher cancer risk.[21]

Metabolic derangements

There are two main hypotheses postulated which might explain the association between diabetes and cancer: the hyperglycaemia hypothesis and the hyperinsulinemia hypothesis. The hyperglycaemia hypothesis[22] suggests that tumour cells grow faster in a high glucose environment, because of their glucose-dependence. Hyperinsulinemia (i.e. elevated blood insulin levels) is often both a result and a driver of insulin resistance[23] and may promote tumour cell growth directly via insulin receptors, or indirectly via the insulin-like growth

factor-1 (IGF-1) receptor. IGF-1, and subsequently the IGF-1 receptor, could act as a growth stimulus for tumour cells and increase tumour growth, invasion and metastasis.[24]

Blood glucose lowering drugs

Along these aforementioned hypotheses, the use of glucose lowering drugs has also been associated with cancer. These drugs include amongst others metformin, insulin (analogues) and DPP-4 inhibitors.

Metformin

Evidence from observational studies suggested that some blood glucose lowering drugs are associated with either increased or reduced risk of cancer. One of these medications is the first-line treatment metformin. Since 2005, different epidemiological studies suggested a reduction in the incidence of cancer with metformin use.[25-27] However, these studies contained important biases that made the results look 'protective'.[28] The more recent epidemiological studies which avoided these biases reported a less protective effect or no association between metformin and the incidence of different cancer types.[29] Currently, many randomised controlled trials (RCTs) are ongoing, investigating whether metformin might be an anti-tumour agent.

Insulin (analogues)

Because of the hyperinsulinemia hypothesis, insulin is studied as a potential cause to explain the increased risk of cancer among people with T2D. Several epidemiological studies[30-32] raised concern that insulin analogues might increase risk of cancer, which lead to a call by the European Medicines Agency (EMA). In 2011, the "Cancer Risk and Insulin analoGues" (CARING) project was initiated to quantify the risk of cancer associated with the use of inulin (analogues). In 2017, they concluded that there was no evidence of a relationship between cancer incidence and use of insulin analogues at follow-up exceeding 5 years.[33]

Incretin-based drugs: DPP-4 inhibitors & GLP-1 receptor agonists

The newer incretin-based drugs are approved by the Food and Drug Administration (FDA) since 2005 and by the EMA since 2006. Studies using the FDA Adverse Event Reporting System (AERS) suggested an increased risk of acute pancreatitis and pancreatic cancer associated with the use of incretin-based drugs.[34, 35] However, the FDA AERS database is based on spontaneous adverse events and henceforward causal relationships cannot be established. Therefore, both the FDA and the EMA independently reviewed all clinical and preclinical data, but in 2014 a final conclusion was not yet reached.[36] A literature review of observational studies concluded that evidence is conflicting and inadequate to conclude whether use of incretin-based therapies indeed increase the risk of pancreatic cancer.[37] Also a meta-analysis of RCTs found no increased risk of pancreatic cancer in people with T2D treated with incretin-based drugs, but pancreatic safety was not the primary outcome of these RCTs and the number of events and follow-up time were limited.[38]

Methodological challenges

Several methodological challenges are important when studying the association between diabetes and/or blood glucose lowering drugs and the incidence of cancer.

Time-related biases include immortal time bias, time-window bias and time-lag bias.[28] Immortal time bias occurs with time-fixed cohort analyses when unexposed time is misclassified as exposed. Time-window bias is introduced when different exposure opportunity time windows between subjects are compared.[28] Timelag bias is present when treatments given at different stages of the disease are compared.[28]

Also, detection bias may sometimes be the main cause for an increased observed cancer incidence among people with diabetes.[39, 40] Detection bias arises when patients in one exposure group have a higher probability of having the study outcome detected, due to increased surveillance, screening or testing of the outcome itself. Indirectly, the latency period of cancer is related to this. The diagnosis of cancer a couple of days after the initiation of a glucose lowering drugs is not likely to be causally related. The latency period differs per cancer and should be accounted for when studying the association.

Furthermore, the speculated carcinogenic mechanisms of blood glucose lowering drugs differ per drug (class). In addition, many treatment changes are required when T2D progresses. Therefore, methods that allow for time-varying exposure should be used to reduce bias.

Additionally, competing risks, such as different site-specific cancers and death due to other causes, should be considered when studying the risk of cancer in patients with T2D.[41]

Different types of cancer vary in relation to their tissue of origin. Therefore, an overall measure of cancer might mask different associations.[42] However, even between different types of one cancer effects can be different.[43]

Outline

The main objectives of the studies described in this thesis were:

- To determine the trend in the prevalence of diabetes in the Netherlands
- To provide more insight into the treatment of people with T2D
- To assess the relationship between different measures of glycaemic exposure and micro- and macrovascular complications
- To contribute to the knowledge regarding the association between T2D and/or blood glucose lowering drugs and characteristics of site-specific cancer

To accomplish these objectives a data platform, the PHARMO DIAbetes, MANagement and Treatment (DIAMANT) cohort, was established to perform studies regarding diabetes (and cancer).

INDEX

In the first part of the thesis **(Part I)** we aimed to provide more insight into the trend in diabetes prevalence and its treatment. It is known that the number of people with T2D increases, but a reliable trend regarding the prevalence of diabetes in the Netherlands is lacking. We determined the trend in the prevalence of diabetes in the Netherlands for the period 1999-2014 and investigated the influence of changes in population demographics on this trend **(Chapter 2)**. Furthermore, it is unknown how people with T2D are treated in actual practice and whether this treatment pattern is in line with the Dutch diabetes guideline. **Chapter 3** provides an overview of the use of glucose lowering drugs over time and the sequential treatment changes among people with T2D in 5 countries in Europe.

The DIAMANT cohort provides a unique source for numerous types of (pharmaco) epidemiological studies in people with diabetes. Chapter 4 and 5 are two examples of such studies. Both studies take full advantage of the longitudinal and large nature of this cohort. **Chapter 4** determines the clinical effectiveness of liraglutide versus basal insulin in terms of changes in HbA_{1c}, weight, BMI, systolic and diastolic blood pressure, and blood lipids, including total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL) over time. In **Chapter 5** the relation between different measures of glycaemic exposure over time and micro- and macrovascular complications is described.

Part II of this thesis focuses on the association between diabetes and/or blood glucose lowering drugs and characteristics of site-specific cancer. With the upcoming use of DPP-4 inhibitors[44] and the concern about a causal association between incretin-based drugs and pancreatitis or pancreatic cancer,[36] we conducted a systematic literature review and meta-analysis to summarise evidence on the association between the use of DPP-4 inhibitors and the incidence of specific cancer types **(Chapter 6)**. Although the EU CARING study[45] concluded that insulin treatment does not seem to impact the association between T2D and breast cancer, it is still possible that insulin (analogues) treatment influences the progression of breast cancer. In **Chapter 7** the association between insulin (analogues) treatment and specific breast cancer characteristics was studied. For colorectal cancer, the prevalence is higher among men than women and also subsite-specific risks differ between men and women. Therefore, we evaluated the impact of T2D on these sex- and subsite-specific risks **(Chapter 8)**. Bias and confounding are common in observational studies. To contribute to the robustness of the association between diabetes and cancer, we investigated whether study design (matched versus non-matched) and censoring or excluding persons with incident diabetes during follow-up might affect this association **(Chapter 9)**.

Finally, this thesis concludes with a general discussion in which the main results of the previous chapters in the context of the current literature are reviewed. Furthermore, methodological considerations, future perspectives and concluding remarks are discussed.

Data sources

PHARMO Database Network

The PHARmacoMOrbidity (PHARMO) Database Network is a population-based network of electronic healthcare databases combining data from different primary and secondary healthcare settings in the Netherlands. These different data sources, including data from general practitioners (GPs), in- and out-patient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms. Detailed information on the methodology and the validation of the used record linkage method can be found elsewhere.[46, 47] The longitudinal nature of the PHARMO Database Network system enables to follow-up more than 4 million (25%) residents of a well-defined population in the Netherlands for an average of ten years. Data collection period, catchment area and overlap between data sources differ. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status and mortality. Other available information is dependent on the data source.

DIAMANT cohort

For this thesis, all people with diabetes were selected from the PHARMO Database Network, resulting in the DIAbetes, MANagement and Treatment (DIAMANT) cohort. Diabetes was defined as (1) a GP recorded diagnosis of diabetes and/or (2) a recorded prescription/ dispensing of blood glucose lowering drugs. This dynamic cohort contains data from 1998 onwards and includes information of more than 500,000 people with diabetes. The information includes, among other things, data from the GP (e.g., diagnoses, drug prescriptions and test results), drug dispensings, hospitalisations and clinical laboratory measurements.

Netherlands Cancer Registry

The Netherlands Cancer Registry (NCR) is maintained by the Netherlands Comprehensive Cancer Organisation[48] and comprises information on newly diagnosed cancer patients in the Netherlands, including cancer diagnosis, tumour staging (according to the TNM-classification developed and maintained by the Union for International Cancer Control [UICC][49]), tumour site (topography) and morphology (histology) (according to the WHO International Classification of Diseases for Oncology [ICD-O-3][50]), co-morbidity at diagnosis and treatment received directly after diagnosis.

Linkage of PHARMO with NCR

Both the PHARMO Database Network and the NCR are recognised as high quality sources for (pharmaco)epidemiological research. For this thesis, data were obtained from the DIAMANT cohort and linked on a patient level to the NCR. The construct and validity of the linkages have been described in detail elsewhere.[47, 51]

INDEX

References

1. IDF Diabetes Atlas. International Diabetes Federation, 2015.
2. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. **BMJ**. 2000; 321: 405-412.
3. van Wijngaarden RPT, Overbeek JA, Heintjes EM, Schubert A, Diels J, Straatman H, et al. Relation Between Different Measures of Glycemic Exposure and Microvascular and Macrovascular Complications in Patients with Type 2 Diabetes Mellitus: An Observational Cohort Study. **Diabetes Ther**. 2017; 8: 1097-1109.
4. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Diabetes mellitus | Cijfers & Context | Huidige situatie. Available from: https://www.volksgezondheidenzorg.info/onderwerp/diabetes-mellitus/cijfers-context/huidige-situatie#node-prevalentie-diabetes-naar-leeftijd-en-geslacht. Accessed July 25, 2018.
5. Rutten GEHM, De Grauw WJC, Nijpels G, Goudswaard AN, Uitewaal PJM, Van der Does FEE, et al. NHG-Standaard Diabetes mellitus type 2 (Tweede herziening). **Huisarts Wet**. 2006; 49: 137-152.
6. Nederlands Huisartsen Genootschap. NHG-Standaard Diabetes mellitus type 2 (Vierde (partiële) herziening). 2018.
7. integraal kankercentrum Nederland. 5-jaarsprevalentie | Alle tumoren; Landelijk; Man & Vrouw. Available from: http://www.cijfersoverkanker.nl/selecties/dataset_1/img5a3bc86d9e89d. Accessed 21 December, 2017.
8. integraal kankercentrum Nederland. The Netherlands Cancer Registry. Available from: www.cijfersoverkanker.nl. Accessed 16 December, 2017.
9. Zanders MMJ. Diabetes and cancer: a dangerous liaison? The reciprocal impact of diabetes and cancer on outcomes with a special focus on drug effects. **NedTijdschrOncol**. 2015; 12: 125-129.
10. Wang P, Kang D, Cao W, Wang Y, Liu Z. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. **Diabetes Metab Res Rev**. 2012; 28: 109-122.
11. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, et al. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. **Eur J Cancer.** 2011; 47: 1928-1937.
12. Zhang ZH, Su PY, Hao JH, Sun YH. The role of preexisting diabetes mellitus on incidence and mortality of endometrial cancer: a meta-analysis of prospective cohort studies. **Int J Gynecol Cancer**. 2013; 23: 294-303.
13. Bao C, Yang X, Xu W, Luo H, Xu Z, Su C, et al. Diabetes mellitus and incidence and mortality of kidney cancer: a meta-analysis. **J Diabetes Complications**. 2013; 27: 357-364.
14. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. **J Natl Cancer Inst**. 2005; 97: 1679-1687.
15. Zhu Z, Zhang X, Shen Z, Zhong S, Wang X, Lu Y, et al. Diabetes mellitus and risk of bladder cancer: a meta-analysis of cohort studies. **PLoS One**. 2013; 8: e56662.

16. Liao S, Li J, Wei W, Wang L, Zhang Y, Li J, et al. Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature. **Asian Pac J Cancer Prev.** 2011; 12: 1061-1065.
17. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. **Cancer Epidemiol Biomarkers Prev.** 2006; 15: 2056-2062.
18. Scheen AJ. Diabetes mellitus in the elderly: insulin resistance and/or impaired insulin secretion? **Diabetes Metab**. 2005; 31 Spec No 2: 5S27-25S34.
19. Gunasekaran U, Gannon M. Type 2 diabetes and the aging pancreatic beta cell. **Aging (Albany NY)**. 2011; 3: 565-575.
20. DeGregori J. Challenging the axiom: does the occurrence of oncogenic mutations truly limit cancer development with age? **Oncogene**. 2013; 32: 1869-1875.
21. De Pergola G, Silvestris F. Obesity as a major risk factor for cancer. **J Obes**. 2013; 2013: 291546.
22. Chang SC, Yang WV. Hyperglycemia, tumorigenesis, and chronic inflammation. **Crit Rev Oncol Hematol**. 2016; 108: 146-153.
23. Shanik MH, Xu Y, Skrha J, Dankner R, Zick Y, Roth J. Insulin resistance and hyperinsulinemia: is hyperinsulinemia the cart or the horse? **Diabetes Care**. 2008; 31 Suppl 2: S262-268.
24. Grimberg A. Mechanisms by which IGF-I may promote cancer. **Cancer Biol Ther**. 2003; 2: 630-635.
25. Decensi A, Puntoni M, Goodwin P, Cazzaniga M, Gennari A, Bonanni B, et al. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. **Cancer Prev Res (Phila)**. 2010; 3: 1451-1461.
26. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. **BMJ**. 2005; 330: 1304-1305.
27. Noto H, Goto A, Tsujimoto T, Noda M. Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. **PLoS One**. 2012; 7: e33411.
28. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. **Diabetes Care**. 2012; 35: 2665-2673.
29. Suissa S. Metformin to Treat Cancer: Misstep in Translational Research from Observational Studies. **Epidemiology**. 2017; 28: 455-458.
30. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. **Diabetologia**. 2009; 52: 1766-1777.
31. Hemkens LG, Grouven U, Bender R, Gunster C, Gutschmidt S, Selke GW, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. **Diabetologia**. 2009; 52: 1732-1744.
32. Jonasson JM, Ljung R, Talback M, Haglund B, Gudbjornsdottir S, Steineck G. Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. **Diabetologia**. 2009; 52: 1745-1754.
33. But A, De Bruin ML, Bazelier MT, Hjellvik V, Andersen M, Auvinen A, et al. Cancer risk among insulin users: comparing analogues with human insulin in the CARING five-country cohort study. **Diabetologia**. 2017; 60: 1691-1703.

INDEX

34. Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. **Gastroenterology**. 2011; 141: 150-156.
35. Feng X, Cai A, Dong K, Bhutada N, Inciardi J. Cancer adverse events associated with dipeptidyl peptidase 4 inhibitors: Data mining of public FDA adverse event reporting system. **Pharmacotherapy**. 2012; 32: e308-e309.
36. Egan AG, Blind E, Dunder K, de Graeff PA, Hummer BT, Bourcier T, et al. Pancreatic safety of incretin-based drugs--FDA and EMA assessment. **N Engl J Med**. 2014; 370: 794-797.
37. Suarez EA, Koro CE, Christian JB, Spector AD, Araujo AB, Abraham S. Incretin-mimetic therapies and pancreatic disease: a review of observational data. **Curr Med Res Opin**. 2014; 30: 2471-2481.
38. Wang H, Liu Y, Tian Q, Yang J, Lu R, Zhan S, et al. Incretin-based therapies and risk of pancreatic cancer in patients with type 2 diabetes: a meta-analysis of randomised controlled trials. **Diabetes Obes Metab**. 2017.
39. De Bruijn KM, Ruiter R, de Keyser CE, Hofman A, Stricker BH, van Eijck CH. Detection bias may be the main cause of increased cancer incidence among diabetics: results from the Rotterdam Study. **Eur J Cancer**. 2014; 50: 2449-2455.
40. Harding JL, Shaw JE, Peeters A, Cartensen B, Magliano DJ. Cancer risk among people with type 1 and type 2 diabetes: disentangling true associations, detection bias, and reverse causation. **Diabetes Care**. 2015; 38: 264-270.
41 Johnson JA, Carstensen B, Witte D, Bowker SL, Lipscombe L, Renehan AG, et al. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. **Diabetologia**. 2012; 55: 1607-1618.
42. Johnson JA, Gale EA. Diabetes, insulin use, and cancer risk: are observational studies part of the solution-or part of the problem? **Diabetes**. 2010; 59: 1129-1131.
43. Zanders MM, van Steenbergen LN, Haak HR, Rutten HJ, Pruijt JF, Poortmans PM, et al. Diminishing differences in treatment between patients with colorectal cancer with and without diabetes: a population-based study. **Diabet Med**. 2013; 30: 1181-1188.
44. Overbeek JA, Heintjes EM, Prieto-Alhambra D, Blin P, Lassalle R, Hall GC, et al. Type 2 Diabetes Mellitus Treatment Patterns Across Europe: A Population-based Multi-database Study. **Clin Ther**. 2017; 39: 759-770.
45. Bronsveld HK, ter Braak B, Karlstad O, Vestergaard P, Starup-Linde J, Bazelier MT, et al. Treatment with insulin (analogues) and breast cancer risk in diabetics; a systematic review and meta-analysis of in vitro, animal and human evidence. **Breast Cancer Res**. 2015; 17: 100.
46. Herings R, Pedersen L. Pharmacy-based Medical Record Linkage Systems. In: Strom B, Kimmel S, Hennessy S, (eds). Pharmacy-based Medical Record Linkage Systems. 5 ed: John Wiley & Sons, Ltd.; 2012. 270-286.
47. van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, Vreugdenhil G, Pruijt JF, Coebergh JW, et al. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. **Eur J Cancer.** 2010; 46: 395-404.

48. Netherlands Comprehensive Cancer Organisation (NCCO). Netherlands Cancer Registry (NCR): record, report, improve and regulate. Available from: https://www.iknl.nl/over-iknl/about-iknl/what. Accessed July 25, 2018.
49. Union for International Cancer Control (UICC). UICC TNM Classification Available from: http://www.uicc.org/resources/tnm. Accessed July 25, 2018.
50. World Health Organization (WHO). WHO International Classification of Diseases for Oncology Available from: http://www.who.int/classifications/icd/adaptations/oncology/en/. Accessed July 25, 2018.
51. Kuiper JG, van Herk-Sukel MPP, van Wijngaarden RPT, Lemmens VEPP, Herings RMC. (2017) Unique opportunities to study the primary care of colorectal cancer. **Value in Health** 20: A741 (Abstract)

CHAPTER 2

Increased prevalence of diabetes in the Netherlands not explained by demographic changes over time: a cross-sectional study over time, 1999-2014

Jetty A. Overbeek, Amber A.W.A. van der Heijden, Ron M.C. Herings, G. Nijpels

Ned Tijdschr Geneeskd.2017;160:D673 [Dutch]

INDEX

Abstract

Introduction: To study the trend in the prevalence of diabetes in the Netherlands for the period 1999-2014 and to investigate the influence of changes in population demographics on this trend.

Methods: The prevalence of treated diabetes during the period 1999 to 2014 was studied using data from the PHARMO Database Network, a network of electronic databases that includes data from public pharmacies for residents of the Netherlands. A person with diabetes was defined as having dispensed two consecutive dispensings of a glucose lowering-drug within six months. Expected and age-adjusted prevalence were calculated per sex to investigate the influence of changes in these population demographics.

Results: The prevalence of diabetes in the Netherlands increased from 1.8% in 1999 to 4.9% in 2014. The increase was more pronounced among men and among persons older than 74 years. Among males 75-84 years of age the prevalence increased from 7.6% in 1999 to 16.5% in 2014. Among females 75-84 years of age this increase was from 8.7% to 16.8%. Only half of the increase was explained by changes in population demographics (i.e. age and sex).

Conclusions: This study showed that the prevalence of diabetes in the Netherlands in the period 1999-2014 more than doubled. Only 44% of this increase was explained by ageing of the society. Future research should concentrate on the identification of those other factors responsible for the increase in order to control diabetes in Western society in the near future.

Introduction

Both the International Diabetes Foundation (IDF) and the World Health Organisation (WHO) reported a global increase in the prevalence of diabetes mellitus.[1,2] Diabetes mellitus is characterized by hyperglycaemia, the primary cause of micro- and macrovascular complications and death among people with diabetes. This is, in part, what makes diabetes such a burden on both the patient and society.[1,2] Some predictions state that diabetes will be one of the diseases with the highest burden by 2030.[3] In 2011, the costs for diabetes care were at least 1.7 billion euro, which equals 1.9% of the total healthcare cost in the Netherlands.[4]
In different Western European countries an increase in prevalence of diabetes was reported over the last decades.[5-9] The prevalence in Denmark increased from 2.8% in 1999 to 5.2% in 2011,[6] in Sweden from 2.7% in 2006 to 4.4% in 2013,[9] and in Germany from 6.6% in 2007 to 8.6% in 2010.[5] Due to ageing of the Dutch population, the increasing prevalence of obesity, a major risk factor of diabetes, the better survival rate and multiple screening initiatives, it is likely that this trend also exists in the Netherlands.[10-14]
According to a report by the National Institute for Public Health and the Environment (RIVM), the absolute number of people with diabetes mellitus in the Netherlands in the period 2000-2007 increased by almost 55%.[4] The RIVM website reports an increase of about 100% for men and 50% for women between 1992 and 2010.[15]
The aim of this study was to calculate the trend in the prevalence of diabetes in the Netherlands for the period 1999-2014 and to investigate the influence of changes in population demographics on this trend. Moreover, the impact of changes in the age and sex distribution of the population on this prevalence was studied.

Materials and Methods

Data collection
The prevalence of diabetes mellitus in the Netherlands between 1999 and 2014 was calculated using a cross-sectional design, which was repeated each year for the duration of the study period. Data for this study was obtained from the Out-patient Pharmacy Database of the PHARMO Database Network as described in more detail previously.[16,17] This database contains information of 3.8 million Dutch inhabitants with respect to dispensed medication prescribed by the general practitioner (GP) or a specialist, including the code of the therapeutic subgroup to which the medicine belongs ('anatomical therapeutic chemical', ATC code) and the dispensing date.

In order to determine the prevalence of diabetes among the population, it is necessary to determine the population size. PHARMO possesses information on the size of the catchment area of the out-patient pharmacies by sex and 5-year age category. Table 1 presents the core

figures of the catchment area of the Out-patient Pharmacy Database on January 1, 2010. For comparison purposes, Table 1 also contains the figures of Statistics Netherlands (CBS) of the Dutch population on 1 January 2010. The age and sex distribution in the catchment area of the Out-patient Pharmacy Database hardly differs from the CBS data. On 1 January 2010, the catchment area of the Out-patient Pharmacy Database contained almost 3.000.000 persons. Almost 50% was male and the majority was 40-65 years old.

Table 1. Distribution of sex and age of the population in the catchment area of PHARMO and the Dutch population - January 1, 2010

	PHARMO	The Netherlands*
Total number of persons; n	2,995,655	16,574,989
Males; %	49.7	49.5
Age; %		
<20 years	22.1	23.7
20-<40 years	24.6	25.3
40-<65 years	37.3	35.7
65-<80 years	11.9	11.4
≥80 years	4.0	3.9

*Source: www.statline.cbs.nl

Study population

For each calendar year, all people who received at least two consecutive dispensings of a blood glucose lowering drug (ATC code A10) within six months prior to the end of the calendar year were selected from the Out-patient Pharmacy Database; these people were defined as having diabetes.

Prevalence of diabetes

The observed, expected and age-adjusted prevalence of diabetes was calculated. The observed prevalence was calculated by dividing the total number of people with diabetes by the total number of persons within PHARMO's catchment area per calendar year, overall, by sex and by age class (0-29 years, 30-54 years, 55-74 years and ≥75 years). The expected prevalence was calculated by multiplying the age- and sex-specific prevalence of 1999 by the number of persons in the following years in those age and sex categories. To adjust for age and sex differences over time, the age-adjusted prevalence per sex was calculated by using direct standardization. Calculation examples can be found in Table S1 (Supporting Information).

Results

Both the catchment area and the absolute number of persons with diabetes increased during the study period. The catchment area (e.g. population size) increased from >2,000,000

in 1999 to nearly 2,600,000 in 2014. The number of persons with diabetes increased from >37,000 in 1999 to nearly 130,000 in 2014. In 1999, the mean age of people with diabetes was 64 (SD: 15) years; 45% was male. In 2014, the mean age was 66 (SD: 15) years and 51% was male.

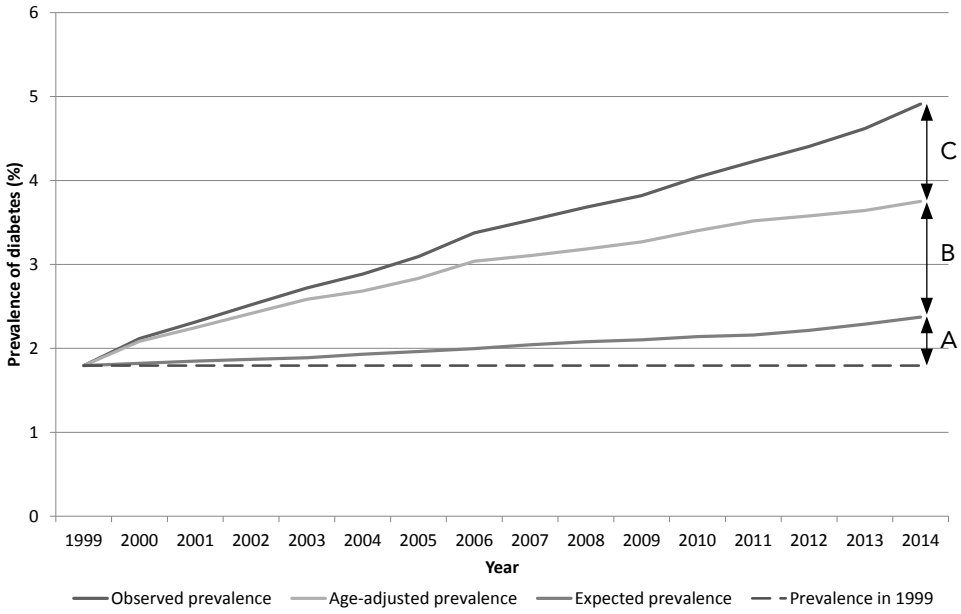


Figure 1 The observed, age-adjusted and expected prevalence of diabetes over time, 1999-2014.

The prevalence of diabetes increased from 1.8% in 1999 to 4.9% in 2014; an increase of 3.1% (Figure 1, observed prevalence). The black dotted line indicates the prevalence in 1999. The expected prevalence shows the prevalence when the age- and sex-specific prevalence would have remained stable from 1999 onwards. The prevalence would then increase from 1.8% in 1991 to 2.4% in 2014; an increase of 0.6% (increase A in Figure 1). The age-adjusted prevalence indicates the prevalence that would have been observed in case of an equal age and sex distribution from 1999 onwards. This increased from 1.8% in 1991 to 3.8% in 2014; an increase of 2.0%.

Increase A in Figure 1 is explained by changes in the age distribution per sex from 1999 onwards. In Figure 1, we indicate the difference between the observed increase and the increase of the age and sex corrected prevalence with C. This difference is also explained by changes in the age distribution per sex. The remaining increase (B in Figure 1) is explained by changes in factors other than the age and sex distribution.

Figure 2 shows the absolute increase of the prevalence of diabetes between 1999 and 2014 by age class (prevalence in 2014 minus prevalence in 1999). The absolute prevalence hardly increased for men and women below the age of 30. For persons aged ≥30 years, the absolute increase was more substantial, for which the increase for persons aged ≥55 years was even more pronounced. The absolute increase for men was highest in the 75-84 year age category, for women it was highest in the 85-89 year age category.

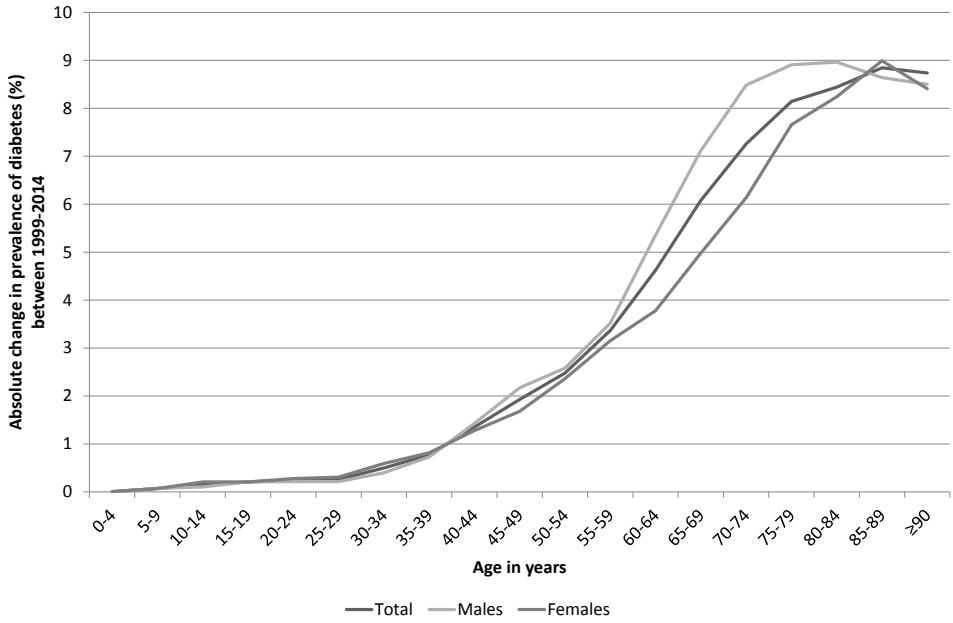


Figure 2 Absolute change in prevalence of diabetes between 1999 and 2014 per age category

Figure 3 presents the prevalence of diabetes between 1999 and 2014 for women (Figure 3a) and men (Figure 3b), stratified by age group. As can be seen in Figure 2 too, the absolute increase in prevalence was the highest among men aged 75-84 years. Relatively, the increase in prevalence was over 115% (from 7.6% in 1999 to 16.5% in 2014). Among women aged ≥75 years the relative increase was almost 95% (from 8.7 to 16.8%). Among the lower age groups the relative increase was >140% for women aged 0-29 years (from 0.15 to 0.36%), almost 95% for men aged 0-29 years (from 0.17 to 0.32%), 170% for women aged 30-54 years (from 0.9 to 2.4%), more than 160% for men aged 30-54 years (from 1.1 to 2.8%), nearly 85% for women aged 55-74 years (from 5.1 to 9.4%) and over 115% for men aged 55-74 years (from 5.0 to 10.8%).

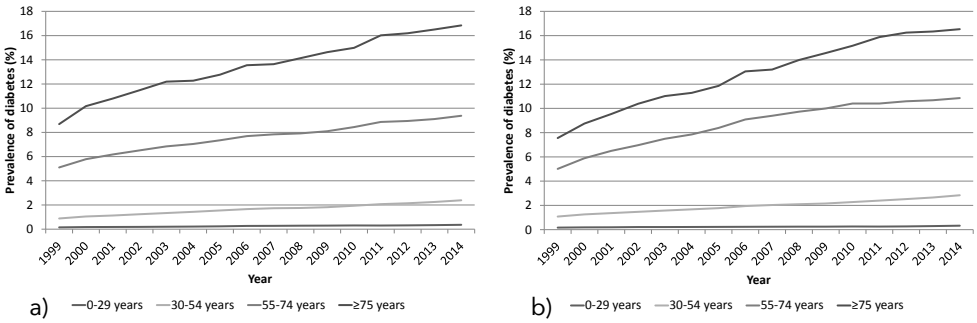


Figure 3 Prevalence of diabetes in the Netherlands between 1999-2014, (a) among women and (b) among men, stratified by age category

Discussion

Prevalence

During 1999-2014, the prevalence of diabetes mellitus increased with almost 75%; from 1.8% in 1999 to 4.9% in 2014. The RIVM reports a prevalence of diabetes of 6.4% in 2014,[18] which is higher than the prevalence in our study. The RIVM's definition of diabetes was 'having a recorded diagnosis for diabetes',[19] while the current study only included persons pharmaceutically treated for diabetes. This will give an underestimation, as a part of the people with diabetes are not or not yet using blood glucose lowering drugs.

Increase in prevalence

A recent publication regarding the global trends in the prevalence of diabetes showed no increase in the Netherlands in the 1980-2014 period.[20] The RIVM website reports an increase of 5.6% per year for men and 2.8% per year for women between 1992 and 2010.[15] In our study, the annual increase for the 1999-2010 period was 9.1% for men and 6.8% for women. The explanations for these differences in annual increase could be related to differences between the studied regions. Prior studies have shown that there are regional differences in risk factors for diabetes – obesity, SES and ethnicity – in the Netherlands.[21-23] The international study measured the prevalence in small populations in Zutphen and Rotterdam (about 1,000 men and 1,000 women per year),[20] whereas the prevalences of the RIVM are based on registrations with information of 29 GP practices from Nijmegen and Maastricht that has been collected in 2012. Our current study based the trend on data from over 200 out-patient pharmacies from across the Netherlands. Another possible explanation is the difference in the definition of diabetes. The international study spoke of diabetes when people had a sober plasma glucose value ≥ 7.0 mmol/l or a diabetes diagnosis, or if they used blood glucose lowering drugs. This broad definition would have ensured that undiagnosed people with diabetes were also counted during the entire study period. As

the number of undiagnosed persons with diabetes decreased,[24,25] this could explain why these researchers did not find an increase. The RIVM defined diabetes as 'having a recorded diagnosis for diabetes'. It is reasonable to assume that after revising the NHG standard 'Diabetes mellitus type 2' in 2006, the number of persons with diabetes according to the definition 'having a recorded diagnosis' differed with the number of patients according to the definition 'receiving dispensings of blood glucose lowering drugs'.[26]

According to Statistics Netherlands, the proportion of people who received dispensings of blood glucose lowering drugs increased from 3.8 in 2006 to 4.6 in 2013.[27] This corresponds with the increase we observed, from 3.4% in 2006 to 4.5% in 2013. The Dutch Journal of Medicine ('Nederlands Tijdschrift voor Geneeskunde', NTvG) published an article regarding the increase in the use of blood glucose lowering drugs from 2.8% in 1999 to 3.6% in 2003.[28] This increase per year corresponds with our results. Data from 53 public pharmacies showed an increase in the use of oral antidiabetic agents from 1.9% in 1999 to 2.4% in 2003.[29] This lower increase per year can possibly be explained due to regional differences.

The annual increase of 0.17% in our country corresponds fairly well with that of other Western European countries.[6,8,9] A number of these studies discuss the differences in prevalence increase per sex and age group. The conclusions correspond to ours. For instance, the prevalence increase in the Swiss study was higher for higher age groups and the increase was also higher for men.[8] In Germany, too, the prevalence increase was higher for higher age groups.[5]

Influence of changes in population demographics

Almost 56% of the total increase in prevalence in our study was explained by changes in age and sex distribution. The other increase (44%) can be attributed to other factors. It was outside the scope of the current study to determine these factors. However, it is known that the prevalence of obesity doubled in the Netherlands in the past 30 years.[11] Another factor might be the publication of the Dutch diabetes guideline for GPs in 2006.[26] This standard advises GPs to perform a blood test every three years for patients with an increased risk of diabetes and to start pharmaceutical treatment with metformin. In the development of the prevalence figures, however, we did not observe a breach with the trend around 2006 (Figure 4).

The prevalence among men increased faster than that among women, which resulted in an equal diabetes prevalence for men and women in 2014. We are unable to explain this. The increase in excess weight and obesity during the period 2000 to 2014 did not differ between men and women.[11] A similar development was observed in Switzerland and Denmark.[6,8]

Strengths and limitations

Our study has some limitations. Persons with diabetes were identified in our study if the pharmacist had provided them with blood glucose lowering drugs more than once. As a

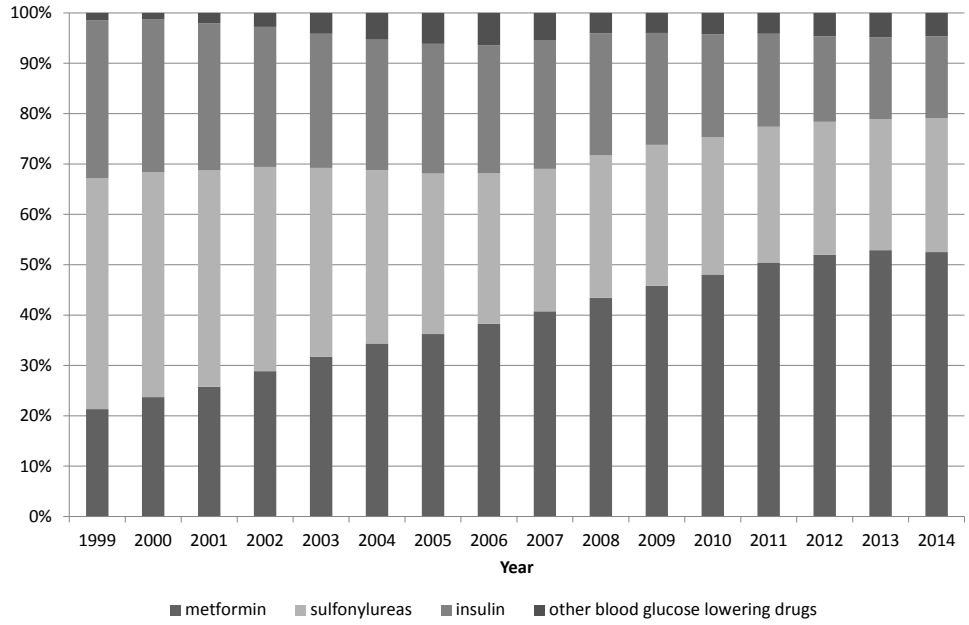


Figure 4. Distribution of different blood glucose lowering drugs during 1999-2014

result, only people with pharmaceutically treated diabetes were included which have led to an underestimation of the actual prevalence, because part of the people with diabetes are not or not yet using blood glucose lowering drugs and because no diagnosis has been provided for a part of the people.[25] However, this underestimation does not affect the course of the prevalence as mapped out by us.

Our study does not distinguish between type 1 and type 2 diabetes. Because about 95% of persons with diabetes has type 2 diabetes, our findings primarily apply to persons with this type of diabetes.

The strength of this study is the use of a major database with recent data that contains up-to-date, reliable information on the situation in the Netherlands. Over time, the same pharmacies have provided data linked to individual patients, which means that the data collection is longitudinal in nature. The use of blood glucose lowering drugs is suitable for the identification of persons with diabetes.[30]

INDEX

Conclusions

The prevalence of diabetes mellitus in the Netherlands has more than doubled in the 1999-2014 period. This increase was more pronounced among men, most visible with the elderly and could only be partially explained by demographic developments. In order to stop the increasing prevalence of diabetes, it is essential to gain a better insight into the other factors that explain this increase.

References

1. International Diabetes Federation (IDF). IDF DIABETES ATLAS, Seventh Edition. http://www.diabetesatlas.org/. Accessed April 18, 2016.
2. World Health Organization. Global report on diabetes. http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf?ua=1. Accessed December 15, 2016.
3. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Een gezonder Nederland - Kernboodschappen van de Volksgezondheid Toekomst Verkenning 2014. https://www.google.nl/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&ved=0ahUKEwiB1Y7Yt-XWAhWH7hoKHXSzD5IQFggxMAI&url=https%3A%2F%2Fwww.rijksoverheid.nl%2Fbinaries%2Frijksoverheid%2Fdocumenten%2Frapporten%2F2014%2F06%2F24%2Feen-gezonder-nederland%2Feen-gezonder-nederland.pdf&usg=AOvVaw2AI1MTUL1ueTifkPP1BIeH. Accessed March 1, 2016.
4. Baan CA, Schoemaker CG, Jacobs-van der Bruggen MAM, et al. Diabetes tot 2025, preventie en zorg in samenhang. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu (RIVM), 2009.
5. Boehme MW, Buechele G, Frankenhauser-Mannuss J, et al. Prevalence, incidence and concomitant co-morbidities of type 2 diabetes mellitus in South Western Germany--a retrospective cohort and case control study in claims data of a large statutory health insurance. **BMC Public Health**. 2015;855.
6. Green A, Sortso C, Jensen PB, et al. Incidence, morbidity, mortality, and prevalence of diabetes in Denmark, 2000-2011: results from the Diabetes Impact Study 2013. **Clin Epidemiol**. 2015;421-430.
7. Hamer M, Kengne AP, Batty GD, et al. Temporal trends in diabetes prevalence and key diabetes risk factors in Scotland, 2003-2008. **Diabet Med**. 2011;5:595-598.
8. Huber CA, Schwenkglenks M, Rapold R, et al. Epidemiology and costs of diabetes mellitus in Switzerland: an analysis of health care claims data, 2006 and 2011. **BMC Endocr Disord**. 2014;44.
9. Norhammar A, Bodegard J, Nystrom T, et al. Incidence, prevalence and mortality of type 2 diabetes requiring glucose-lowering treatment, and associated risks of cardiovascular complications: a nationwide study in Sweden, 2006-2013. **Diabetologia**. 2016.
10. Garssen J. Demografie van de vergrijzing. http://www.cbs.nl/NR/rdonlyres/9F0DEB0A-8529-4951-92B2-1DF29352C75F/0/2011k2b15p15art.pdf. Accessed May 30, 2016.
11. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Percentage volwassenen met overgewicht en obesitas van 1981-2012. https://www.volksgezondheidenzorg.info/onderwerp/overgewicht/cijfers-context/trends#node-trend-overgewicht-bij-volwassenen. Accessed March 1, 2016.
12. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Trend levensverwachting bij geboorte. https://www.volksgezondheidenzorg.info/onderwerp/levensverwachting/cijfers-context/trends#node-trend-levensverwachting-bij-geboorte. Accessed December 15, 2016.

13. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Preventie van diabetes. https://www.volksgezondheidenzorg.info/onderwerp/diabetes-mellitus/preventie-zorg/preventie. Accessed December 15, 2016.
14. Statistics Netherlands. Bevolking naar leeftijd (op 1 januari) voor de periode 1999-2015. http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=37296NED&D1=14-18,22&D2=49-65&HDR=G1&STB=T&VW=T. Accessed March 1, 2016.
15. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Trend prevalentie diabetes. https://www.volksgezondheidenzorg.info/onderwerp/diabetes-mellitus/cijfers-context/trends-en-toekomst#!node-trend-prevalentie-diabetes. Accessed March 22, 2016.
16. Herings RMC, Pedersen L. (2012). Pharmacy-based Medical Record Linkage Systems (Fifth edition ed.). John Wiley & Sons, Ltd.
17. Zanders MM, Haak HR, van Herk-Sukel MP, et al. Impact of cancer on adherence to glucose-lowering drug treatment in individuals with diabetes. **Diabetologia**. 2015;5:951-960.
18. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Diabetes mellitus | Cijfers & Context | Huidige situatie. https://www.volksgezondheidenzorg.info/onderwerp/diabetes-mellitus/cijfers-context/huidige-situatie#node-prevalentie-diabetes-huisartsenpraktijk. Accessed July 18, 2016.
19. Netherlands institute for health services research (NIVEL). Incidentie/prevalentie | NIVEL. http://www.nivel.nl/nl/NZR/over-nivel/methode/Incidentie-prevalentie. Accessed July 18, 2016.
20. NCD Risk Factor Collaboration. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. **Lancet**. 2016;10027:1513-1530.
21. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Sociaaleconomische status | Regionaal & Internationaal | Regionaal. https://www.volksgezondheidenzorg.info/onderwerp/sociaaleconomische-status/regionaal-internationaal/regionaal. Accessed July 22, 2016.
22. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Niet-westerse allochtonen per gemeente 2010-2040 - Nationale Atlas Volksgezondheid. http://www.zorgatlas.nl/beinvloedende-factoren/demografie/etniciteit/niet-westerse-allochtonen-per-gemeente-2010-2040/. Accessed March 1, 2016.
23. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Grote regionale verschillen in overgewicht, roken en alcoholgebruik. http://www.rivm.nl/Documenten_en_publicaties/Algemeen_Actueel/Nieuwsberichten/2013/Grote_regionale_verschillen_in_overgewicht_roken_en_alcoholgebruik. Accessed July 22, 2016.
24. Mooy JM, Grootenhuis PA, de Vries H, et al. Prevalence and determinants of glucose intolerance in a Dutch caucasian population. The Hoorn Study. **Diabetes Care**. 1995;9:1270-1273.
25. van 't Riet E, Alssema M, Rijkelijkhuizen JM, et al. Relationship between A1C and glucose levels in the general Dutch population: the new Hoorn study. **Diabetes Care**. 2010;1:61-66.

26. Rutten GEHM, De Grauw WJC, Nijpels G, et al. NHG-Standaard Diabetes mellitus type 2 (Tweede herziening). **Huisarts Wet**. 2006;3:137-152.
27. Statistics Netherlands. Personen met verstrekte geneesmiddelen; leeftijd en geslacht. http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=81071NED&D1=a&D2=0&D3=0&D4=35&D5=0-7&HDR=T,G4,G1&STB=G3,G2&VW=T. Accessed July 21, 2016.
28. Langendam MW, Hooijkaas C, Piepenbrink JF. Toenemend gebruik van geneesmiddelen voor diabetes mellitus in Nederland, 1998-2003. **Ned Tijdschr Geneeskd**. 2006;25:1396-1401.
29. Lub R, Denig P, van den Berg PB, et al. The impact of new insights and revised practice guidelines on prescribing drugs in the treatment of Type 2 diabetes mellitus. **Br J Clin Pharmacol**. 2006;6:660-665.
30. Hirsch AG, Scheck McAlearney A. Measuring Diabetes Care Performance Using Electronic Health Record Data: The Impact of Diabetes Definitions on Performance Measure Outcomes. **Am J Med Qual**. 2014;4:292-299.

Supporting Information

Table S1. Calculation example: observed, expected and age-adjusted prevalence for men, ≥55 years

Age category (years)	1999				2007				2014			
	D	N	q	Y	D	N	q	Y	D	N	q	Y
55-59	2,054	54,880	25.78	0.037	6,804	103,677	27.50	0.066	7,264	100,014	23.48	0.073
60-64	2,132	46,252	21.72	0.046	8,086	84,273	22.35	0.096	9,167	91,981	21.59	0.100
65-69	2,342	40,368	18.96	0.058	7,025	64,310	17.06	0.109	11,004	85,180	19.99	0.129
70-74	2,149	31,809	14.94	0.068	6,614	51,605	13.69	0.128	9,144	60,002	14.08	0.152
75-79	1,657	22,857	10.74	0.072	5,284	37,872	10.04	0.140	7,177	44,416	10.43	0.162
80-84	868	10,745	5.05	0.081	2,966	23,042	6.11	0.129	4,838	28,385	6.66	0.170
≥85	466	6,000	2.82	0.078	1,417	12,289	3.26	0.115	2,672	16,034	3.76	0.167
Total	**11,668**	**212,911**	**100**	**0.055**	**38,196**	**377,068**	**100**	**0.101**	**51,266**	**426,011**	**100**	**0.120**

D = number of people with diabetes by age category; N = population by age category; q = age distribution; Y = age-specific prevalence.

Expected prevalence: Per age category, the expected number of persons with diabetes was based on the age-specific prevalence in 1999. This results in the number of persons with diabetes if the age-specific prevalence since 1999 had not changed. The expected prevalence for 2007 is: (0.037 * 103,677) + (0.046 * 84,273) + (0.058 * 64,310) + (0.068 * 51,605) + (0.072 * 37,872) + (0.081 * 23,042) + (0.078 * 12,289) / 377,068 = 5.4% for men aged ≥55 years. For 2014 the expected prevalence is 5.6% for men aged ≥55 years.

Observed prevalence: Per year, the total number of people with diabetes (Σ D) was divided by the total population (Σ N). In 1999 the observed prevalence was 11,668 / 212,911 = 5.4% for men aged ≥55 years. For 2007 the observed prevalence was 10.1% and for 2014 12.0%.

Age-adjusted prevalence: For each year after 1999, the age-specific prevalence was weighted with the age distribution of 1999. This results in the number of people with diabetes if the age distribution had not changed since 1999. For 2007, the age-adjusted prevalence is: (0.2578 * 0.066) + (0.2172 * 0.096) + (0.1889 * 0.109) + (0.1494 * 0.128) + (0.1074 * 0.140) + (0.0505 * 0.129) + (0.0282 * 0.115) = 10.2% for men aged ≥55 years and for 2014 11.8% for men aged ≥55 years.

INDEX

CHAPTER 3

Type 2 diabetes mellitus treatment patterns across Europe: a population-based multi-database study

Jetty A. Overbeek, Edith M. Heintjes, Daniel Prieto-Alhambra, Patrick Blin, Régis Lassalle, Gillian C. Hall, Francesco Lapi, Elisa Bianchini, Niklas Hammar, Irene D. Bezemer, Ron M.C. Herings

Clin Ther. 2017 Apr;39(4):759-770. doi: 10.1016/j.clinthera.2017.02.008

Abstract

Purpose: The aim of this study was to determine the similarities and differences of type 2 diabetes mellitus (T2DM) treatment patterns in daily practice in five European countries and whether these reflect differences in the guidelines.

Methods: Prescriptions for drugs used in diabetes during a 5-year study period were obtained from electronic databases. Patients initiating T2DM treatment during the study period were included. A SAS analysis tool was developed to create episodes of use of drug classes, which resulted in treatment patterns.

Findings: A total of 253,530 persons initiating T2DM treatment during the study period were included; 52% to 55% were male, and the mean age ranged from 62 to 67 years. Metformin was the most common initial treatment in all countries. After initial therapy, most patients in the Netherlands, Spain, and the United Kingdom switched to a combination of metformin + a sulfonylurea derivative (SU). In Italy, metformin in combination with an SU was outnumbered by "other treatment," mainly because of repaglinide use. In France, treatments including dipeptidyl peptidase-4 inhibitors were most frequent as second- and fourth-line treatment. Metformin monotherapy was again most commonly observed as third treatment in all countries. Fourth treatment was a combination of metformin + an SU in the Netherlands and Spain; while in the United Kingdom and France, dipeptidyl peptidase-inhibitors were the most frequently used fourth line of treatment.

Implications: This study provides a comprehensive overview of T2DM treatment patterns among patients initiating T2DM treatment in five European countries. There were differences, especially regarding the uptake of newer incretin-based treatments, which are usually prescribed as a second and/or third treatment in agreement with local guidelines. These variations reflect the differences between the national guidelines of these countries.

INDEX

Introduction

Changes in lifestyle and ageing of the population have led to an increasing prevalence of type 2 diabetes mellitus (T2DM) worldwide.[1-3] Hyperglycaemia is a risk factor for excess microvascular and macrovascular complications and mortality.[4] Although initial glycaemic control may be achieved through diet and exercise,[5] pharmacological intervention is necessary at some stage in most patients.

Most European countries have a national guideline on T2DM, and the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have developed a consensus approach to the management of hyperglycaemia to help guide healthcare providers in choosing the most appropriate interventions for their patients with T2DM.[6] At the time of conducting this study, 8 different blood glucose lowering drug classes were approved for the treatment of T2DM in Europe: metformin, sulphonylurea derivatives (SUs), α-glucosidase inhibitors (AGIs), thiazolidinediones (TZDs), dipeptidyl peptidase-4 inhibitors (DPP-4i), meglitinides, glucagon-like peptide-1 receptor agonists (GLP-1RAs), and insulin.

The international guidelines for use of these therapies share the common goal of preventing and treating symptoms and microvascular and macrovascular complications by achieving/sustaining glycaemic control.[6-11] In general, these guidelines recommend starting pharmacological treatment with metformin and intensification of treatment as the disease progresses or treatment fails to achieve or sustain the glycaemic goals (Table). However, the guidelines differ in recommendations regarding the type of intensification. Disparities in guideline recommendations can differ for several reasons, such as the influence of professional bodies and characteristics of health care systems.[12] Intensification of treatment by adding an SU is well established in the ADA/EASD consensus[6] and the Netherlands,[8] Spain,[9] and the United Kingdom.[7] The guidelines from Italy[10] and France,[11] however, are less strict and offer multiple treatment options as early as the second line of treatment. Guidance for third-line treatment also differs, with strict approaches recommended by the ADA/EASD consensus, the Netherlands and the United Kingdom (e.g., by adding insulin), compared with the addition of a third oral drug, GLP-1RA, or insulin in Spain.

Furthermore, the newer incretin-based classes of DPP-4i and GLP-1RAs, which were introduced in the last decade, have different places in the various guidelines,[6-11] partly due to limited safety information and the higher cost of these classes. With these variations in mind, the present study analysed the similarities and differences of T2DM treatment patterns in actual practice in 5 European countries and whether these reflected differences in the international guidelines.

Table. Overview of step-wise pharmacologic treatment of type 2 diabetes mellitus (T2DM) according to national guidelines per country.

Step	ADA and EASD*,[6]	The Netherlands[8]	Italy[10]	Spain[9]	France[11]	United Kingdom[7]
1	Metformin	Metformin	Metformin	Metformin In case of contraindications or intolerance, SU should be considered	Metformin/AGI	Metformin Consider SU if not overweight, or metformin is not tolerated or contraindicated, or a rapid therapeutic response is required because of hyperglycaemic symptoms
2	+Insulin/SU	+SU/pioglitazone SU for patients with a BMI <27 kg/m^2 and patients with a BMI ≥27 kg/m^2 a nd no CVD or with heart failure, pioglitazone for patients without evidence for or increased risk of heart failure	+TZD/GLP-1RA/DPP-4i/SU or glinides At each step the early initiation of insulin therapy is stated as a possibility	+SU Alternatives are TZD, glinides, AGI and DPP-4, depending on patient characteristics	"Bi-therapy"	+SU Consider insulin for patients with erratic lifestyle and consider DPP-4i or TZD if there is a significant risk of hypoglycaemia or an SU is contraindicated or not tolerated
3	Metformin + intensive insulin	+Basal insulin	+TZD/GLP-1RA/DPP-4i/basal insulin	+A third oral drug (SU, TZD, glinides, AGI, DPP-4i)/GLP-1RA/insulin	"Tri-therapy"	+Insulin Consider sitagliptin (DPP-4i) or TZD if insulin is unacceptable and consider exenatide (GLP-1RA) if BMI ≥35 kg/m^2 or if BMI <35 kg/m^2 and insulin is unacceptable or weight loss would benefit other comorbidities)
4		Intensify insulin	Metformin + SU or glinides + basal insulin		Insulin + OAD	Increase insulin dose Consider pioglitazone + insulin if a TZD has previously had a marked glucose lowering effect or blood glucose control is inadequate with high-dose insulin

ADA, American Diabetes Association; AGI, α-glucosidase inhibitors; BMI, body mass index; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; EASD, European Association for the Study of Diabetes; GLP-1RA, glucagon-like peptide-1 receptor agonist; OAD, oral antidiabetic; SU, sulphonylureas derivatives; TZD, thiazolidinedione. *Only the tier 1 algorithm is described as this is the preferred route of therapy for most patients with T2DM.

Materials and Methods

Setting

All data for this observational cohort study were obtained from population-based electronic health care databases from 5 European countries: the PHARMO Database Network[13] in the Netherlands, the Health Search Longitudinal Patient Database[14,15] in Italy, the Sistema d' Informació per al Desenvolupament de la Investigació en Atenció Primària[16,17] in Catalonia, Spain, the Echantillon Généraliste de Bénéficiaires[18] in France, and The Health Improvement Network[19,20] (THIN) in the United Kingdom. The PHARMO Database Network is a population-based, patient-centric data tracking system that currently comprises demographic and health care databases, including patient demographic characteristics, mortality, drug dispensing, hospital morbidity, clinical laboratory, pathology findings, and general practitioner information. The Health Search Longitudinal Patient Database contains patient demographic details that are linked by using an encrypted patient code with medical records, drug prescription information, prevention records, hospital admission, and date of death. The Sistema d' Informació per al Desenvolupament de la Investigació en Atenció Primària database includes common clinical variables (e.g., smoking, alcohol drinking, body mass index, blood pressure), primary care laboratory results (e.g., glycosylated haemoglobin [HbA_{1c}], glucose), pharmacy invoice data, and hospital discharge information.

THIN is an observational database of electronic health care records from primary care practices throughout the United Kingdom. Demographic and administrative data, primary and secondary care diagnoses, and prescription treatments are routinely recorded against date in individual patient records. The Echantillon Généraliste de Bénéficiaires is a permanent random sample with a 1/97 representation of the nationwide claims and hospitalization database, (Système National d'Information InterRégimes de l'Assurance Maladie SNIIRAM), which covers >98% of the French population from birth (or immigration) to death (or emigration), even if a subject changes occupations or retires. It includes general characteristics, outpatient reimbursed health care, and discharged summary for all public and private hospitalizations. Data from all countries except France were electronic health records from routine primary care. Data from France were collected for health insurance reimbursement claims.

Study population

The study population included all adult patients with T2DM initiating glucose lowering-treatment, further referred to as T2DM treatment, during the most recent 5-year period that was available in each database at the time of analysis: January 1, 2007, to December 31, 2011, for the Netherlands, Spain, Italy, and France, and from January 1, 2008, to December 31, 2012, for the United Kingdom. Patients with T2DM were defined as having a diagnosis code for T2DM, or at least 2 prescriptions for blood glucose-lowering drugs, excluding insulins within a 6-month period at any time in the available medication records.

The date of the first prescription for T2DM treatment during the study period was defined as the index date. Patients with T2DM were required to have ≥12 months of continuous enrolment immediately preceding the index date; patients with any prescription for blood glucose-lowering drugs in these 12 months were excluded because they were not treatment initiators. Patients with a recorded diagnosis code for type 1 diabetes mellitus or for gestational diabetes were also excluded. All included patients were followed from the index date to the end of registration in the database, death, or end of study period, whichever occurred first.

Data management

All data were analysed at the site of the database holder by using a common data model. To ensure a homogeneous analysis within the different databases, an SAS analysis tool (SAS Institute, Inc, Cary, North Carolina) creating treatment patterns was developed and validated. All database holders were asked to prepare specified input files adhering to the common data model that complied with the tool.

Treatment pattern

The tool converted prescription records (1 record per prescribed drug including date, encrypted patient identifier and Anatomical Therapeutic Chemical code) first into 1 record per drug class per calendar month, and then subsequently into episodes of use of each drug class and combination therapies, and ultimately into aggregated therapies. Formulations of oral combinations were split into their individual drugs before processing.

Drug classes

To characterize treatment patterns, the following drug classes were identified from the electronic records: metformin, SUs, TZDs, DPP-4i, GLP-1RAs, insulin, and "other treatment" (e.g., AGI, metaglinides).

Episodes of use

Because the duration of use of an individual prescription was not available in all databases, an algorithm was used to create treatment episodes. Prescriptions for blood glucose-lowering drugs may cover up to 3 or even 6 months. However, low compliance or short time referral to specialist care may lead to a longer interval between prescriptions recorded in primary care. Therefore, prescriptions of the same drug class which were ≤9 months apart were considered to represent an episode of uninterrupted use of that drug class. If no subsequent prescription was found within 9 months, treatment with the drug class was assumed to have stopped 1 month after the last prescription date. Multiple episodes per patients, even of the same drug class, were possible. Overlapping episodes of multiple drug classes were interpreted as concomitant use (i.e., combination therapy). However, if the start of an episode of 1 drug class occurred in the month after the last prescription of another class, this occurrence was interpreted as a switch, and the prior class was cut short at the

time of start of the episode of the new class. The time to change was defined as the duration of each treatment (either monotherapy or combination therapy).

Aggregation of drug classes
For presentation purposes, it was necessary to decrease the large number of different treatments. The following therapies were aggregated in the following order: 1) all insulin-containing combination therapies; 2) the DPP-4i-containing therapies; and 3) the GLP-1RA-containing therapies. The remaining therapies (i.e., metformin, SU, TZD, other treatment) or combinations thereof were shown separately if they represented >5% of each study population; they were otherwise aggregated into the group "other".

Statistical analyses
Proportions of all patients using specific glucose-lowering drug classes were determined in January of each calendar year of the study period (cross-sectional) according to country. For the patients initiating T2DM treatment, their general characteristics, proportion of patients per aggregated T2DM therapy, and switching destinations per treatment sequence are reported descriptively per country, presenting proportions for categorical variables, and mean with SD or median with interquartile range for continuous variables.
The median time to change in treatment was estimated per therapy per country using Kaplan-Meier survival analysis, using change in treatment as the outcome event. Patients were right-censored at the end of follow-up in the database records or end of the study period. The time at which 50% of the patients had changed therapy was presented as the median time to treatment change.
All data were analysed by using SAS version 9.2 or higher (SAS Institute Inc).

Results

General characteristics
A total of 253,530 persons initiating T2DM treatment during the study period were included: 19,512 (8%) from the Netherlands, 25,018 (10%) from Italy, 145,882 (58%) from Spain, 6,721 (3%) from France and 56,397 (22%) from the United Kingdom. Male patients represented 52% to 55% of the study population, and the overall mean age at initiation ranged from 62 years (France) to 67 years (Italy). Median follow-up was ~3 years (ranging from 2 years (Italy) to 4 years [Spain]).

Overall use of glucose lowering drug classes
Across all countries, metformin (alone or in combination) was the most commonly used drug and its use increased over time (Figure 1). Second most common drug class was SUs, although, in contrast to metformin, their use decreased over time. The use of insulin was stable during the study period and very limited in France compared with the other countries

(5%-8% in France vs 17%-22% in the other countries). TZD use decreased during the study period except in Italy, especially in 2011, when rosiglitazone was withdrawn in all countries, and all TZDs were withdrawn in France. Clear differences between the participating countries were seen for incretin-based treatments. DPP-4i use substantially increased during the study period in France (0% to 27%), the United Kingdom (<1% to 9%) and Spain (0% to 9%), but its use remained limited in the Netherlands (4%) and Italy (2%). For GLP-1RA use, although the proportions were low in all countries, a similar pattern was observed: the use increased substantially in France and the United Kingdom over time, while the uptake was limited in the Netherlands, Italy, and Spain.

Proportion of patients on specific T2DM treatments per treatment sequence

At least 1 change to another T2DM treatment was observed during the study period for 32% (Italy) to 46% (Spain) of newly treated patients. The proportion of patients with at least 1 change was the highest among the country with the longest follow-up.

Metformin monotherapy was the most common initial treatment in all countries (ranging from 65% in Italy to 88% in the United Kingdom) (Figure 2). As a second treatment, combination of metformin and an SU was most common in the Netherlands (47% of patients changing treatment), the United Kingdom (45%), and Spain (24%). Treatment cessation after first treatment, temporary or not, was often observed (11% in the United Kingdom to 35% in Italy) and was highly variable depending on the amount of follow-up available in the countries. In Italy, the second treatment often consisted of other treatments (22%), which is an aggregated group consisting of many diverse treatments. DPP-4i monotherapy or in combination with other therapies was common in France for the second through fourth treatment (32% up to 42%). Also in the United Kingdom, DPP-4i monotherapy or combination therapy was common as a third treatment class (28%). However, metformin monotherapy was most commonly used as third treatment, ranging from 33% in France to 48% in Spain. In the Netherlands, a common third treatment was any combination with insulin (15%); in Italy, other treatment was the second most common third treatment (17%). Fourth treatment was most often a combination of metformin and an SU in the Netherlands (27%) and in Spain (21%), in the United Kingdom and France, the fourth line was DPP-4i monotherapy or combination therapy (29% and 42%, respectively). In Italy, the fourth most common treatment was other treatment (27%).

Switching destinations per sequential treatment

Patients with metformin monotherapy as the initial treatment most often switched to a combination of metformin and an SU in the Netherlands (56%), the United Kingdom (48%), and Spain (29%), but to DPP-4i monotherapy or combination therapy in France (41%) and to other treatment in Italy (24%) (Figure 3A). When the second treatment was a combination of metformin and SU, patients most often resumed metformin in the Netherlands (38%), Spain (34%), and Italy (42%) (Figure 3B). The same approach was observed for patients with a temporary stop after their initial treatment (62%-80% of the patients switched [back] to

metformin). In France and the United Kingdom, patients most often switched to a DPP-4i monotherapy or combination therapy (both 35%). Patients with DPP-4i monotherapy or combination therapy as second treatment (which was the most common second treatment in France) most often remained on DPP-4i when they switched but combined with another treatment (ranging from 44% in Italy to 64% in France) (Figure 3C). In the Netherlands, Spain, and the United Kingdom, patients with metformin as their third treatment most often switched to a combination of metformin and an SU (44%, 32%, and 38%, respectively); in France and Italy, metformin users switched to DPP-4i monotherapy or combination treatment (46%) or other treatment (27%).

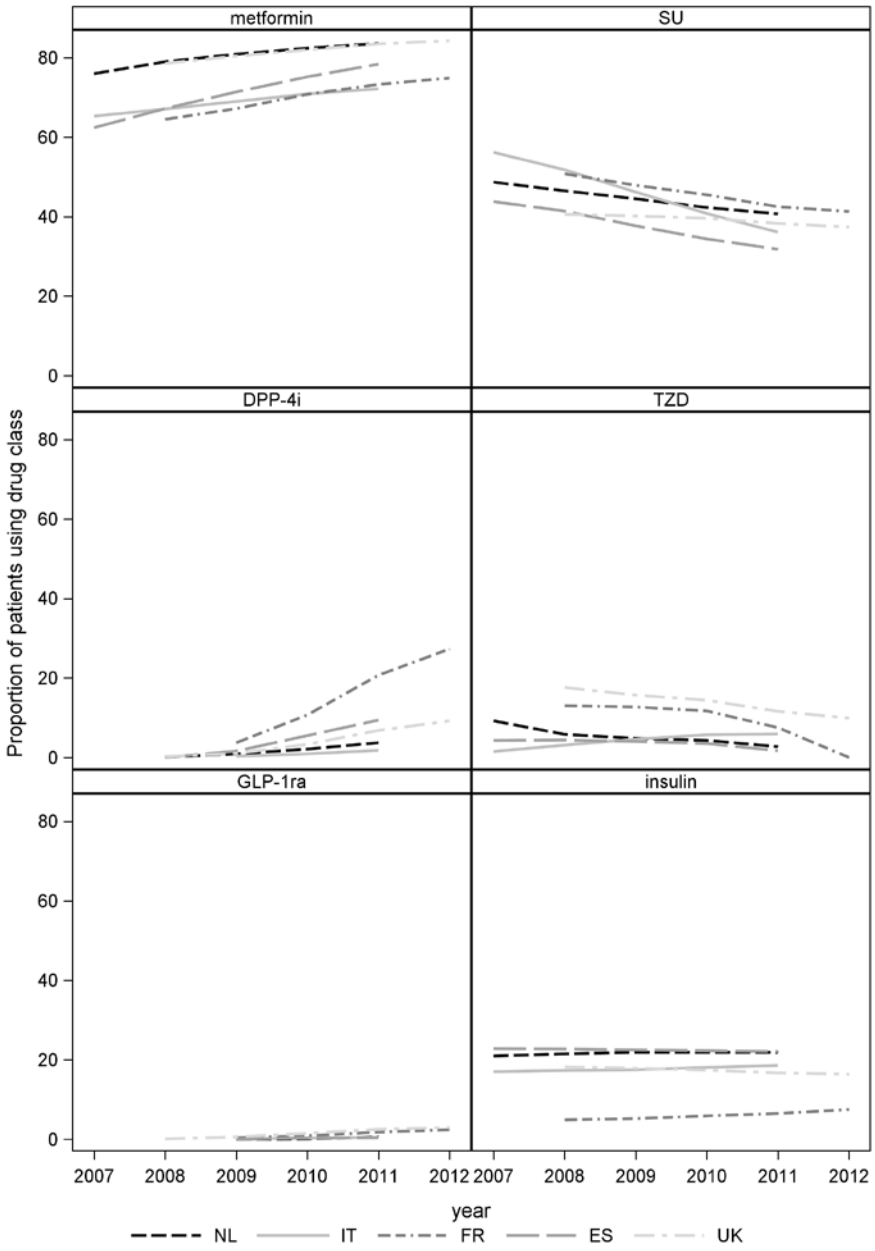


Figure 1 Overall use of glucose-lowering drug class per year per country. Per year, proportions of the drug classes combined add up to > 100% because oral combination formulations were split into their individual drugs before processing. DPP-4i = dipeptidyl peptidase-4 inhibitors; ES = Spain; FR = France; GLP-1RA = glucagon-like peptide-1 receptor agonists; IT = Italy; NL = the Netherlands; TZD = thiazolidinediones; SU = sulfonylurea derivatives; UK = United Kingdom.

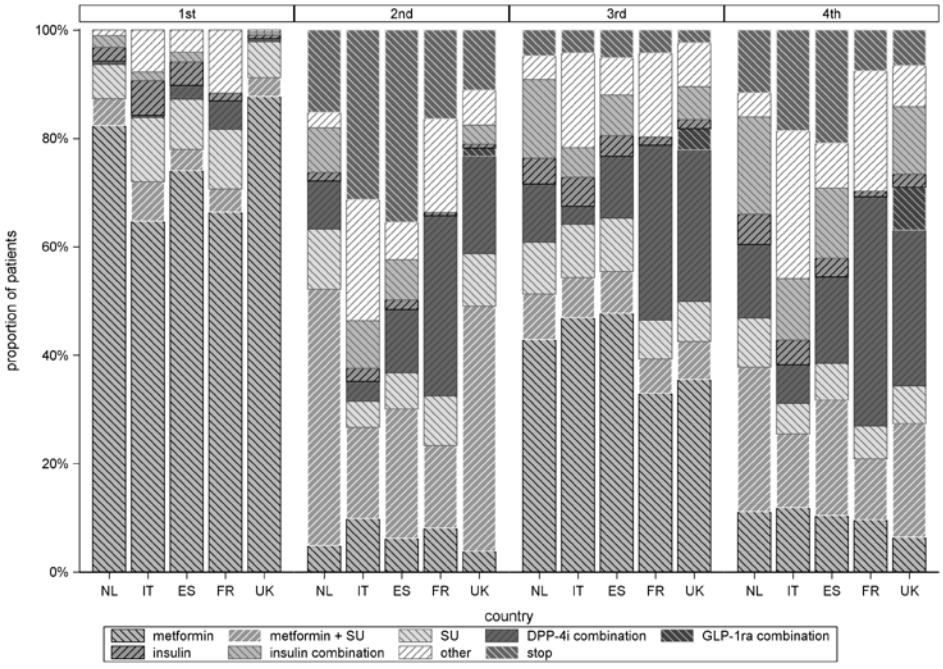


Figure 2 Switching destinations per treatment during study period per country. DPP-4i = dipeptidyl peptidase-4 inhibitors; ES = Spain; FR = France; GLP-1RA = glucagon-like peptide-1 receptor agonists; IT = Italy; NL = the Netherlands; TZD = thiazolidinediones; SU = sulfonylurea derivatives; UK = United Kingdom.

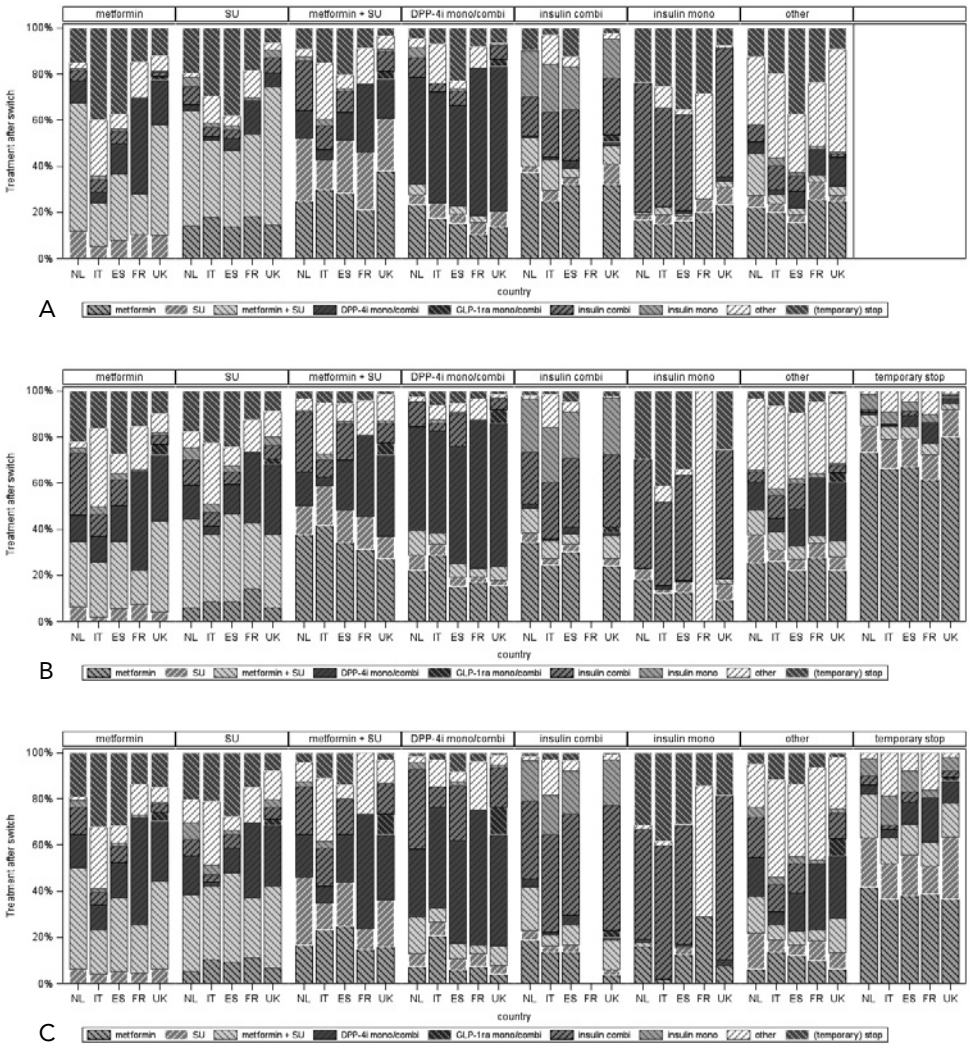


Figure 3 Proportion of patients undergoing specific type 2 diabetes mellitus (T2DM) treatments per treatment per sequence per country. (A) Switching destination from first treatment to second treatment; (B) switching destination from second treatment to third treatment; (C) switching destination from third treatment to fourth treatment. Switching from glucagon-like peptide-1 receptor agonists (GLP-1RA) was not presented because this treatment was only available for the United Kingdom and included only 16 patients. DPP-4i = dipeptidyl peptidase-4 inhibitors; ES = Spain; FR = France; IT = Italy; NL = the Netherlands; TZD = thiazolidinediones; SU = sulfonylurea derivatives; UK = United Kingdom.

Time to change

In all countries, the median time until treatment change declined with the number of sequential changes (Figure 4). Differences in median time spent on treatment between countries were large for the first treatment (40 months for the United Kingdom, 37 months for the Netherlands, 31 months for Italy, 24 months for Spain and 22 months for France) but smaller for subsequent treatments (second treatment ranged from 16-23 months, third from 15-21 months, and fourth from 13-17 months).

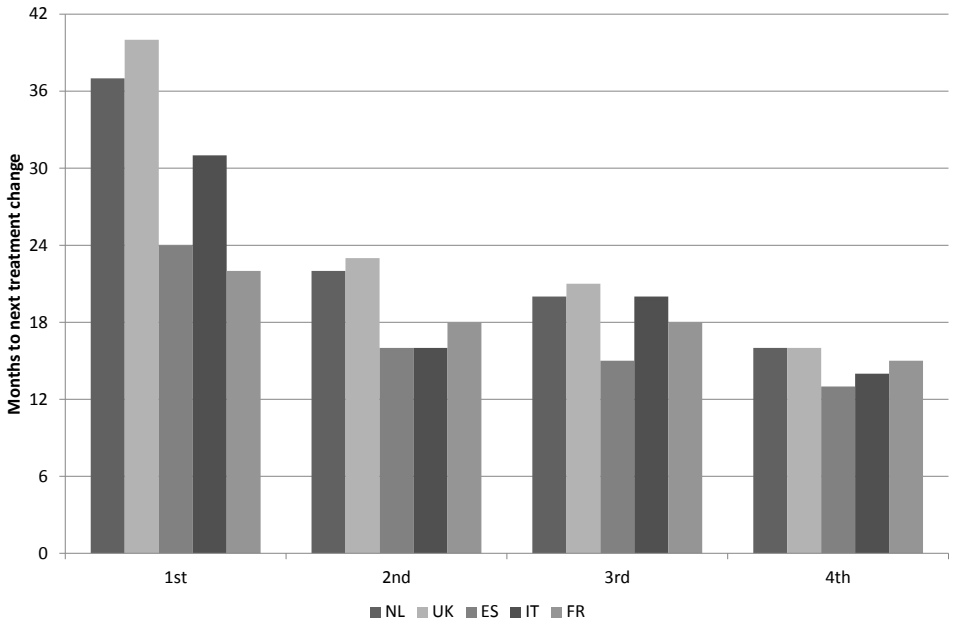


Figure 4 Median time to change of sequential treatments per country. ES = Spain; FR = France; IT = Italy; NL = the Netherlands; UK = United Kingdom.

Discussion

This study describes the overall use of glucose-lowering drug classes and treatment patterns in 5 European countries. Metformin was the most common initial treatment in all countries, as recommended by international guidelines.[6-11] After initial therapy, the choice of drug classes differed between the countries. The combination of metformin and an SU was most common in the Netherlands, Spain and the United Kingdom, which is in line with the ADA/EASD consensus[6] and the respective national guidelines.[7-9] The guidelines from Italy[10] and France[11] are less strict and offer multiple treatment options as early as the second line of

treatment. This approach is reflected in the greater variation in second-line treatment that was observed.

Although the use of incretin-based treatments is discouraged in the Netherlands,[21] these newer treatments were observed in all countries. The proportion of DPP-4i users was particularly high in France, even as a second line of treatment. Furthermore, use of GLP-1RAs substantially increased in the United Kingdom and France; these differences can also be partly explained by the guidelines. GLP-1RAs is mainly recommended/reimbursed for patients with a minimum body mass index threshold, and because the proportion of patients who are overweight is the highest in the United Kingdom, as reported by the World Obesity Federation,[22] this guide explains the observation for the United Kingdom. For France, the explanation would be the lack of guidance as the French guideline only states "bi-therapy".

An interesting finding was that many patients switched back and forth between monotherapy and dual therapy, despite the recommendation of guidelines to intensify when glycaemic control remains insufficient. Even with our lenient definition of treatment continuation (allowing repeat prescriptions as much as 9 months apart), many interruptions were observed. Whether treatment interruptions and de-intensifications reflect noncompliance, intolerance, or physicians de-intensifying treatment because of reaching glycaemic control could not be determined from this study.

The median time to change differed between the countries. However, this cannot be interpreted in terms of quality of care as the reason for change was not available. A short time to change in treatment may indicate that patients are actively managed and receive more intensive treatment because the prior treatment proved ineffective. However, a short time to change may also indicate that patients did not tolerate the prior treatment very well. A long time to change in treatment might indicate inertia when change is actually due, or it may indicate that patients' disease is well controlled and a change in treatment is not needed. Because HbA_{1c} level and other possible triggers for treatment change were not documented for all patients in all databases, it was outside the scope of the present study to assess the factors associated with time to change in treatment.

Differences in rates of microvascular and macrovascular complications and HbA_{1c} levels at time of diagnosis and at time of treatment change might also hamper interpretation of the differences in time to change between countries. In another study,[23] large variations in HbA_{1c} levels at the start of treatment intensification between the countries were observed. In general, patients in the Netherlands seem to intensify treatment at a lower HbA_{1c} level (7.8%-8.0%), whereas patients in the United Kingdom intensified treatment at a higher HbA_{1c} level (8.5%-9.1%).

To our knowledge, no other multicountry study has been published regarding T2DM treatment patterns using a similar approach. Most studies did not follow patients over time but simply presented cross-sectional data per year, and most studies predated our study period, thereby excluding new drug classes such as the DPP-4i and GLP-1Ras.[24-29] Per country, overall use of glucose-lowering drug classes over time was more often studied in these other trials, and results similar to our study were observed. During 2004 to 2013, the use of

metformin and SUs in the Netherlands increased, while the use of TZDs decreased; the use of DPP-4i remained low.[30] Use of metformin did not change during the 2010-2012 period in Italy, use of SUs and TZDs decreased, and use of GLP-1RAs and DPP-4i increased.[31] In Spain, metformin was the most common drug class, and DPP-4i use increased (in relative terms) the most during the 2008-2012 period.[32] In France, the use of metformin increased during 2007-2013, and all TZD and some SU treatments were replaced by DPP-4i and to a much lesser extend by GLP-1Ras.[33] For the 2006-2010 period, metformin as an initial treatment increased and SUs as initial treatment decreased in the United Kingdom.[34] Another study also showed a stable prevalence of insulin use between 2000 and 2013 and a decrease in TZD use since 2007.[35]

Strengths and limitations

A major strength of this study is its design. This multicountry observational and longitudinal study regarding T2DM treatment patterns used the same statistical program applied to all countries (common data model), which ensured a homogenous analysis along the countries. More than 250,000 patients initiating T2DM treatment during 2007/2008-2011/2012 time periods were included.

Because recent data were not available during the study, there is limited information regarding newer T2DM treatments. We did expect differences regarding the uptake of these newer treatments, particularly in second line and beyond, as current guidelines differ in recommending these newer drugs. Furthermore, patients included in the study could only be described in terms of demographic characteristics. Unfortunately, clinical information such as HbA_{1c} levels, microvascular and macrovascular complications, co-medications, or comorbidities was not available for all 5 countries.

A proxy for duration of use of a prescription was used as the actual duration was not available in all databases. An algorithm was used assuming continued use of a drug class as long as there was a repeat prescription within 9 months. This method was used to avoid creation of gaps in treatment if patients were temporarily treated by a specialist but continued their original treatment because not all specialist prescriptions may be visible in the general practitioner databases. However, in most countries the general practitioner is the main treating physician for patients with T2DM.

For the present study, drug classes for the treatment of T2DM were defined a priori by the PHARMO Institute: metformin, SU, TZD, DPP-4i, GLP-1RA, other oral antidiabetic drugs, and insulin. The drug class of other oral antidiabetic drugs combined meglitinides, guar gum, benfluorex, pramlintide and AGIs. However, the use of meglitinides and AGIs differed per country; for example, acarbose is more often prescribed in France, where it is mentioned as an alternative to metformin as first-line treatment.[11] Furthermore, repaglinide was often prescribed in Italy. Generally, meglitinides are suggested as an alternative to SUs only in cases of high risk of SU-induced hypoglycaemia, as meglitinides have a higher cost and a more frequent dosing schedule compared with SUs. This approach made comparisons between the countries regarding this group difficult.

Future directions

This study provides a comprehensive overview of T2DM treatment patterns among patients initiating T2DM treatment in 5 European countries. It may also serve as background material when interpreting other diabetes studies across Europe and to put these in perspective. In addition, because our study does not provide reasons for initiating or discontinuing treatment, further research should focus on this area of interest.

Conclusions

Initial T2DM treatment is similar in the Netherlands, Italy, Spain, France and the United Kingdom. Differences concern the uptake of newer incretin-based treatments, which are usually prescribed as a second and/or third line of treatment. Because approval, availability, and reimbursement were very similar between the selected countries; the different treatment patterns observed are probably driven by guidelines and/or local organization of diabetes care (e.g., the presence of diabetes clinics and/or diabetes disease management programs). The newer treatments had not yet find their place in all guidelines during the study period. For countries with national guidelines not in line with the ADA/EASD consensus (i.e., Italy and France), our results suggest that these countries prefer to follow their national guidelines.
Apparently, despite 1 European regulatory authority which centrally decides whether a medicine is authorized in Europe, actual T2DM treatment differs per country. These data are of interest to EU health care commissioners and policy makers because they contain key information on sources of heterogeneity in the treatment of T2DM throughout European Union member states.

Acknowledgements

This work was supported by a grant from AstraZeneca Pharmaceuticals LP.
The authors thank all the health care providers contributing information to the different databases included in this study.
All authors contributed substantially to conception and design, acquisition of data, or analysis and interpretation of data. Drs. Overbeek, Dr. Heintjes, and Dr. Bezemer drafted the manuscript and Dr. Prieto-Alhambra, Blin, Lassalle, Hall, Lapi, Bianchini, Hammar, and Herings revised it critically for important intellectual content. All authors gave their final approval of the final manuscript.

Conflict of interest

No limitations were set with regard to the conduct of the study and the writing of the manuscript by the study sponsors.

Drs. Overbeek, Dr. Heintjes, Dr. Bezemer and Dr. Herings are employees of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related health care authorities and several pharmaceutical companies. Dr. Prieto-Alhambra's research group and/or department have received unrestricted research grants from Bioberica, AMGEN, and Servier Laboratoires. Dr. Blin and Dr. Lassalle are employees of The Bordeaux PharmacoEpi (BPE)-CIC 1401, an academic research team that performs financially supported studies for public and private partners, including several pharmaceutical companies. Dr. Hall has been a member of the Advisory Group of the THIN database and has received funding for research and consultancy from a number of pharmaceutical companies and from charities. Dr. Lapi provided consultancies in protocol preparation and data analysis for epidemiological studies for AMGEN, Sanofi and Eli-Lilly. Dr. Bianchini has no conflict of interest to disclose. Dr. Hammar is an employee of AstraZeneca. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

INDEX

References

1. Chittleborough CR, Grant JF, Phillips PJ, et al. The increasing prevalence of diabetes in South Australia: the relationship with population ageing and obesity. **Public Health**. 2007;2:92-99.
2. Andersson T, Ahlbom A, Magnusson C, et al. Prevalence and incidence of diabetes in Stockholm County 1990-2010. **PLoS One**. 2014;8:e104033.
3. Geiss LS, Wang J, Cheng YJ, et al. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980-2012. **JAMA**. 2014;12:1218-1226.
4. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. **BMJ**. 2000;7258:405-412.
5. American Diabetes Association. Standards of medical care in diabetes--2014. **Diabetes Care**. 2014;S14-80.
6. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. **Diabetologia**. 2009;1:17-30.
7. Vigneri P, Frasca F, Sciacca L, et al. Diabetes and cancer. **Endocr Relat Cancer**. 2009;4:1103-1123.
8. Rutten GEHM, De Grauw WJC, Nijpels G, et al. NHG-Standaard Diabetes mellitus type 2 (Tweede herziening). **Huisarts Wet**. 2006;3:137-152.
9. Ariz Arnedo MJ, Artola Menéndez S, Barutell Rubio L, et al. Práctica clínica en la DM2. Barcelona, 2011.
10. (SID) AMDA-SIdD. Standard italiani per la cura del diabete mellito tipo 2, 2011.
11. Agence française de sécurité sanitaire des produits de santé (afssaps) et Haute Autorité de Santé (HAS). Traitement médicamenteux du diabète de type 2 (Actualisation), recommendations de bonne pratique. http://www.formindep.org/IMG/pdf/recos_diabete-2006.pdf. Accessed 24 February, 2016.
12. Burgers JS, Bailey JV, Klazinga NS, et al. Inside guidelines: comparative analysis of recommendations and evidence in diabetes guidelines from 13 countries. **Diabetes Care**. 2002;11:1933-1939.
13. PHARMO Institute for Drug Outcomes Research. http://www.pharmo.com. Accessed 22 April, 2016.
14. Cricelli C, Mazzaglia G, Samani F, et al. Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases. **J Public Health Med**. 2003;3:254-257.
15. Filippi A, Vanuzzo D, Bignamini AA, et al. The database of Italian general practitioners allows a reliable determination of the prevalence of myocardial infarction. **Ital Heart J**. 2005;4:311-314.

16. Garcia-Gil Mdel M, Hermosilla E, Prieto-Alhambra D, et al. Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). **Inform Prim Care**. 2011;3:135-145.
17. Vinagre I, Mata-Cases M, Hermosilla E, et al. Control of glycemia and cardiovascular risk factors in patients with type 2 diabetes in primary care in Catalonia (Spain). **Diabetes Care**. 2012;4:774-779.
18. Tuppin P, de Roquefeuil L, Weill A, et al. French national health insurance information system and the permanent beneficiaries sample. **Rev Epidemiol Sante Publique**. 2010;4:286-290.
19. The Health Improvement Network (THIN) database. https://www.ucl.ac.uk/pcph/research-groups-themes/thin-pub/database. Accessed 29 April, 2016.
20. Blak BT, Thompson M, Dattani H, et al. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. **Inform Prim Care**. 2011;4:251-255.
21. Verduijn T, Janssen PG. NHG-Standpunt DPP-4-remmers en GLP-1-agonisten. http://www.diabetes2.nl/uploads/user/rest/DPP-4-remmers_en_GLP-1-agonisten.pdf. Accessed 22 April, 2016.
22. World Obesity Federation. Adult overweight and obesity in the European Union (EU28) based on Measured Height and Weight. http://www.worldobesity.org/site_media/library/resource_images/EU_28_Adults_Feb_2015_.pdf. Accessed 22 April, 2016.
23. Overbeek JA, Heintjes EM, Hall GC, et al. Factors Associated with T2DM Treatment Choice Across Europe. **Value Health**. 2015;7:A600.
24. Boyc KS, Yurgin N, Lage MJ. Trends in the prescription of antidiabetic medications in France: evidence from primary care physicians. **Adv Ther.** 2007;4:803-813.
25. Langendam MW, Hooijkaas C, Piepenbrink JF. [The increase in the use of drug treatment for diabetes mellitus in the Netherlands, 1998-2003]. **Ned Tijdschr Geneeskd**. 2006;25:1396-1401.
26. Baviera M, Monesi L, Marzona I, et al. Trends in drug prescriptions to diabetic patients from 2000 to 2008 in Italy's Lombardy Region: a large population-based study. **Diabetes Res Clin Pract**. 2011;1:123-130.
27. Arrieta FJ, Calvo MJ, Perez A, et al. [Prevalence and consumption of medication in diabetes mellitus in Madrid (1996-2002)]. **Rev Clin Esp**. 2006;3:117-121.
28. Leal I, Sammon C, Masclee GMC, et al. Trends of use of non-insulin blood glucose lowering drugs in Europe and USA. **Pharmacoepidemiol Drug Saf**. 2015;S1:106-107 (Abstract).
29. Leal I, Sammon C, Masclee GMC, et al. Patterns of use of incretin-based therapies in Europe and USA. **Pharmacoepidemiol Drug Saf**. 2015;S1:106 (Abstract).
30. Torre C, Guerreiro J, de Oliveira Martins S, et al. Patterns of glucose lowering drugs utilization in Portugal and in the Netherlands. Trends over time. **Prim Care Diabetes**. 2015.

31. Rafaniello C, Arcoraci V, Ferrajolo C, et al. Trends in the prescription of antidiabetic medications from 2009 to 2012 in a general practice of Southern Italy: a population-based study. **Diabetes Res Clin Pract**. 2015;1:157-163.
32. Mancera-Romero J, Hormigo-Pozo A, Fernandez-Arquero J, et al. [Use of glucose-lowering drugs in a primary care setting in Malaga during the years 2008-2012]. **Semergen**. 2014;1:4-11.
33. Simon D, Dallongeville J, Charbonnel B, et al. Patterns of Pharmacological Treatment in Type 2 Diabetes in France in 2013. **Value Health**. 2015;7:A599.
34. Maguire A, Mitchell BD, Ruzafa JC. Antihyperglycaemic treatment patterns, observed glycaemic control and determinants of treatment change among patients with type 2 diabetes in the United Kingdom primary care: a retrospective cohort study. **BMC Endocr Disord**. 2014;73.
35. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. **BMJ Open**. 2016;1:e010210.

INDEX

CHAPTER 4

Clinical effectiveness of liraglutide vs basal insulin in a real-world setting: evidence of improved glycaemic and weight control in obese patients with type 2 diabetes

Jetty A. Overbeek, Edith M. Heintjes, Eline L. Huisman, Christian K. Tikkanen, Arnout W. van Diermen, Fernie J.A. Penning-van Beest, Ron M.C. Herings

Diabetes Obes Metab. 2018 May 3. doi: 10.1111/dom.13335

Abstract

Aim: To compare real-world anti-diabetic treatment outcomes over 12 months in obese type 2 diabetes mellitus (T2DM) patients who previously received oral anti-diabetic (OAD) therapy and then initiated a first injectable therapy with liraglutide or basal insulin.

Materials and methods: This was a retrospective, propensity score-matched, longitudinal cohort study using real-world data (January 2010 to December 2015) from the Dutch PHARMO Database Network. Adult obese (body mass index [BMI] ≥35 kg/m^2) T2DM patients with ≥2 dispensing dates for liraglutide or basal insulin therapy (BOT) were selected. The primary endpoint was the change in HbA_{1c} from baseline during 12 months of follow-up. The secondary endpoints were the changes in weight, BMI, and cardiovascular risk factors from baseline. Clinical data were analysed using descriptive statistics and compared using mixed models for repeated measures.

Results: Obese T2DM patients (1,157) were matched (liraglutide cohort n=544, BOT cohort n=613). From 3 months onwards, glycaemic control improved in both cohorts but improved significantly more with liraglutide than with BOT (12 months: -12.2 mmol/mol vs. -8.8 mmol/mol; p=0.0053). In addition, weight and BMI were significantly lower for treatments with liraglutide vs. BOT (12 months: -6.0 kg vs. -1.6 kg and -2.1 kg/m^2 vs. -0.5 kg/m^2; p<0.0001 for both). No significant differences were seen in changes in cardiovascular risk factors.

Conclusions: The results of this real-world study in matched obese T2DM patients showed that liraglutide was more effective than BOT for HbA_{1c} control and weight/BMI reductions. Patients were more likely to maintain glycaemic control over time when initiating liraglutide than when initiating BOT.

INDEX

Introduction

In 2013, 56 million people were diagnosed with diabetes in Europe, with a further increase of 10 million projected by 2035.[1] Diabetes is associated with disability and is a major cause of premature mortality.[2] Compared with that in the general population, the risk of coronary heart disease is 2 to 4 times higher in men and women with type 2 diabetes mellitus (T2DM), respectively.[3] Half of people with T2DM die prematurely from a cardiovascular cause, while ~10% die of renal failure. Compared with non-overweight people, overweight and obese people with T2DM are at an even greater risk of coronary heart disease, stroke, cardiovascular disease, and all-cause mortality,[4] and their weight negatively impacts their lives and perception of health status.[5]

Diabetes is therefore one of the world's leading causes of healthcare expenditure and of economic loss in society. The American Diabetes Association (ADA) calculated that people with diabetes have healthcare expenditure 2.3 times higher than that for the same population without diabetes.[6] While the care for people with diabetes who experience macro- and microvascular complications is particularly costly to the healthcare system[7,8]; metabolic complications may explain ~11% of the extra costs of the disease.[6] In the Netherlands, the total economic burden of diabetes was calculated to be €6.8 bn in 2016.[9] More than half (~€4.0 bn) of these costs are indirect and are related to productivity losses, welfare payments and complications, with another €2.9 bn spent on disease care and treatment of complications.

In a joint position paper, both the ADA and the European Association for the Study of Diabetes have recommended a stepwise addition of one of five classes of anti-hyperglycaemic drugs to metformin when patients fail to achieve their glycated haemoglobin (HbA_{1c}) target.[10,11] When considering pharmacological treatments for obese patients with T2DM, it is suggested that medications should be chosen to promote weight loss or to be weight neutral, to improve insulin resistance and to reduce blood pressure and blood lipid levels.[12,13] Fear of weight gain and hypoglycaemia are risk factors known to delay intensification of antidiabetic treatment.[14,15] Obtaining tight glycaemic control with certain antidiabetic medications, particularly insulin and sulphonylureas, may paradoxically be accompanied by an increased risk of weight gain and hypoglycaemia,[16] while this effect is not observed for antidiabetic treatment with glucagon-like peptide 1 receptor agonists (GLP-1RAs), sodium-glucose co-transporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors. The explanation for these differences is linked to the mode of action of different classes of antidiabetic drugs. Randomized clinical trials (RCTs) have shown that intensification with a long-acting GLP-1RA, compared with basal insulin supported oral therapy (BOT) only, leads to improved glycaemic control, weight reduction, and a lower risk of hypoglycaemia.[17] Although RCTs provide evidence for the efficacy and safety of diabetes treatments, these trials are limited by their design, setting, and patient characteristics. Hence, the results cannot be generalized directly to the real-world clinical setting.[18] An evidence gap exists, therefore, between RCTs and real-world practice that warrants studies using real-world data.

INDEX

To our knowledge, there are no real-world studies that compare liraglutide with BOT in a matched population with T2DM. The primary objective of the present study, therefore, was to compare the outcomes of liraglutide and BOT treatments over a period of 12 months after treatment initiation in obese people with T2DM (body mass index [BMI] ≥35 kg/m²) in the Netherlands. The study focused on patients who were on prior oral antidiabetic (OAD) therapy and who initiated their first injectable therapy with liraglutide or BOT. The secondary objective was to perform the same analysis over a period of 24 months, or until the time point at which the cohort size was still >50% of the size at baseline (≤50% attrition).

Materials and Methods

INDEX

Study design

This was a retrospective, propensity score-matched, real-world, longitudinal cohort study in people with T2DM with a BMI ≥35 kg/m². Data were obtained from the PHARMO Database Network.[19] Patients who started treatment with liraglutide or BOT between January 1, 2010 and December 31, 2015 in the Netherlands were included. HbA_{1c} change from baseline to 12 months and to either 24 months or 50% attrition was the primary endpoint. The secondary endpoints were changes in absolute weight, BMI, systolic (SBP) and diastolic blood pressure (DBP), and blood lipids, including total, LDL and HDL cholesterol. The proportion of patients who reached the target HbA_{1c} at 3, 6, 9, and 12 months was also assessed. The HbA_{1c} targets were ≤53 mmol/mol (≤7.0%) for patients aged <70 years, ≤58 mmol/mol (≤7.5%) for older patients with a diabetes duration <10 years, and ≤64 mmol/mol (≤8%) for all remaining patients in line with the Dutch treatment guidelines.[20]

Data source

The PHARMO Database Network is a population-based network of probabilistically linked electronic healthcare databases collecting real-world data from multiple primary and secondary healthcare settings, representing up to a quarter of the population spread throughout the Netherlands.[19] Out-patient pharmacy drug dispensing and clinical laboratory test results, which were prescribed and ordered by both specialists and general practitioners (GPs), were complemented with the GP records of 1.1 million patients. The GP Database comprises data from electronic patient health records recorded by GPs and includes information on diagnoses, symptoms, clinical assessments, laboratory test results, referrals to specialists and prescriptions. Ethics committee approval was not obtained; in the Netherlands, this approval is not required for database research with anonymous data.

Study population

From the Out-patient Pharmacy Database, data from patients using liraglutide or BOT were included based on the following inclusion criteria: (1) BMI ≥35 kg/m² for BOT users (this criterion was not specified for liraglutide users as BMI ≥35 kg/m² and specialist initiation

are required for GLP-1RA reimbursement in the Netherlands. As a result, BMI information is often missing in the GP records but assumed to be ≥35 kg/m^2); (2) at least a 6-month history of outpatient data previous to the cohort entry date; (3) new use of liraglutide or BOT, defined as having no dispensing history for these treatments prior to the cohort entry date and ≥2 consecutive dispensing dates of liraglutide or BOT after the cohort entry date; (4) prior OAD therapy; and (5) ≥1 measurement of the analysed data in the year prior to the cohort entry date, as well as ≥1 measurements between 12 weeks after the cohort entry date and the end of follow-up. The criterion of ≥1 measurement after 12 weeks was added to ensure that the analyses were based on patients for whom it could be reasonably expected that a treatment effect could be observed.

The individual cohort entry date (baseline) was the date of the first dispensing of liraglutide or BOT. Patients were followed from baseline to 24 months or until the time point at which the cohort size was still >50% of the size at baseline (≤50% attrition) to prevent too much bias from differential attrition rates. Reasons for ending the observation earlier were change in the type of treatment, end of database registration (lost to follow-up), or death. For users of liraglutide, change in treatment was defined as cessation of use or add-on of any insulin or another GLP-1RA; for BOT users, change in treatment was defined as either cessation of BOT use or add-on of any other insulin or a GLP-1RA. Changes in concomitant OAD drugs were allowed in both cohorts.

A series of steps were followed to select eligible patients and form two matched cohorts of patients receiving either liraglutide or BOT (Figure 1). Propensity score matching was performed to minimize selection bias attributable to the more restrictive reimbursement conditions for GLP-1RA than for BOT.[21]

Study cohort definition

To ensure comparable treatment cohorts and to include as many patients as possible, selected liraglutide and BOT users were matched per outcome, resulting in eight matched cohorts. Matching (ratio 1:1) was based on propensity scores determined with logistic regression modelling with categorical variables (Table S1) in order to allow the contribution of clinical variables that were not known for all patients but were not the main outcome of interest. Variables significantly associated with the probability of receiving liraglutide (univariate type III $P < .05$) were included in a backward selection process, retaining the variables that were significantly associated in the multivariate model ($P < .05$). Age was always included in the propensity score. The variable "concomitant OAD treatment at start of liraglutide or BOT" was an exact matching criterion outside the scope of the propensity score. Patients were matched on the logit of the propensity score using callipers with a width equal to 0.2 of the standard deviation (SD).

Statistical analysis

Descriptive statistics (arithmetic mean and SD; median and interquartile range [IQR]; counts [n] and proportions [%]) were calculated for demographic variables, for changes in clinical

variables from baseline to 3, 6, 9, and 12 months, and for the 50% attrition time point. For each 3-month interval, the last measurement was included in the analyses. No lag time was required for the 3-month time point. Mixed-effect models repeated measurements analyses were used to compare changes in clinical variables from baseline between patients in the liraglutide and BOT cohorts. All available data were used in the analysis in order to estimate the mean change vs baseline values for each clinical outcome at each time interval. The mixed model allowed missing time points and used available information from the patients with missing time points and similar patients to estimate the least square means (LSM) at each time point.[22]

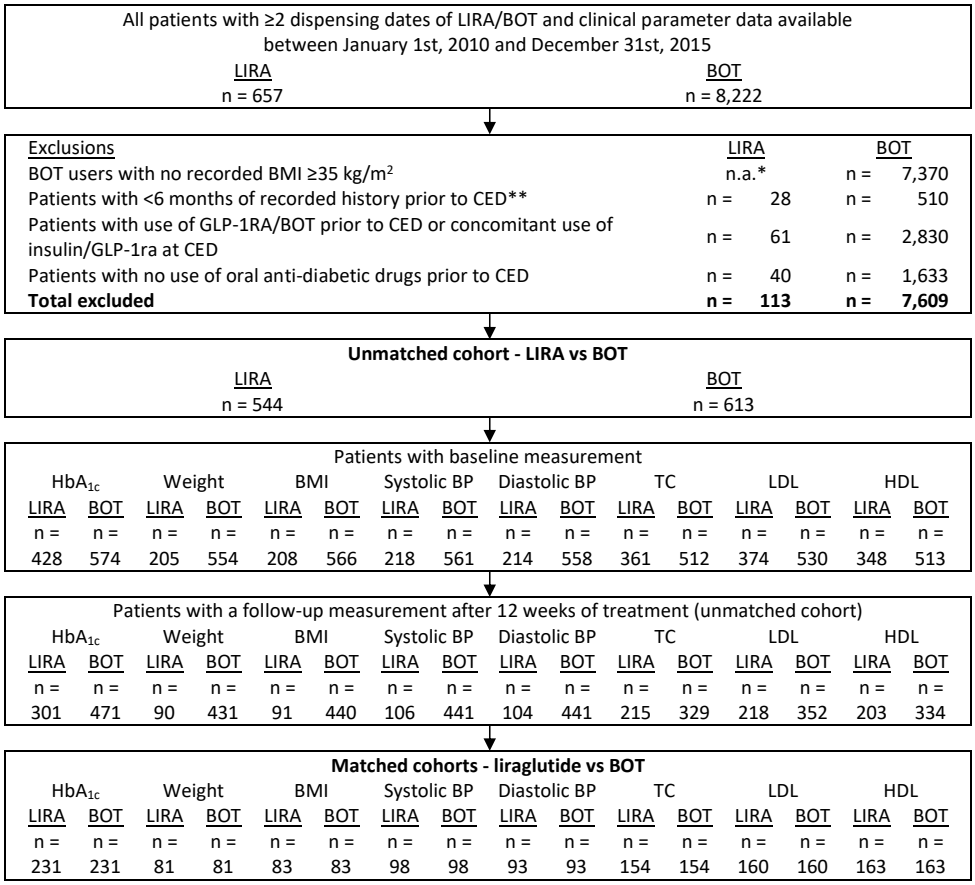
The model included the patient number as a random effect. Fixed effects included study drug, time interval, interaction between study drug and time interval, age (continuous), gender, baseline value of the modelled outcome, and prior OAD treatment. Other covariates were added as categorical fixed effects if they were significantly associated ($P < .05$) with the modelled outcome. Modelled point estimates with 95% CIs for the change over time adjusted for confounders were calculated. Point estimates of the difference in LSM with 95% CIs were obtained for every 3 months of follow-up.

The HbA_{1c} targets were ≤53 mmol/mol (≤7.0%) for patients aged <70 years, ≤58 mmol/mol (≤7.5%) for older patients with a diabetes duration <10 years, and ≤64 mmol/mol (≤8%) for all remaining patients.20 The proportion of patients reaching their HbA_{1c} target was assessed per 3-month interval. For missing time points, the last observation was carried forward until the next available time point or the end of follow-up for each patient.

All data were analysed using SAS programs in SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC, USA) and conducted in Windows using SAS version 9.4.

Results

Between January 1, 2010 and December 31, 2015, 8879 patients with ≥2 consecutive dispensing dates for either liraglutide (n=657) or BOT (n=8222) were identified in the PHARMO Database Network. Of the insulin users, 7609 (93%) were excluded, mainly because of missing BMI data for 90% of all insulin users. For liraglutide users, prior use of insulin or other GLP-1RAs accounted for 9% of the 17% who were excluded; 34% of basal insulin users also used fast-acting insulin. The minimal recorded history of 6 months necessary for baseline assessments was lacking in 4% of liraglutide and 6% of basal insulin users. The failure of oral therapy required for reimbursement of GLP-1RAs could not be determined for 6% of GLP-1RA and 20% of basal insulin users. After the general inclusion and exclusion criteria were applied, 544 liraglutide and 613 BOT users were included in the unmatched cohort (Figure 1). Further stepwise selection resulted in two matched cohorts of subjects on liraglutide or BOT per outcome. This selection resulted in 231 subjects per cohort for the primary endpoint of change from baseline in HbA_{1c}. Matching resulted in comparable cohorts. In Figure S1, the logit of the propensity score distribution is given for HbA_{1c}, weight and BMI.



*The exclusion criteria 'no recorded BMI ≥35 kg/m^2, was only applied to BOT users, as it is a reimbursement criteria for glucagon-like peptide-1 receptor agonist (GLP-1RA) use in the Netherlands. **Cohort entry date (CED) = date of the first dispensing of LIRA or BOTH within the study period. Abbreviations: BMI, body mass index; BP, blood pressure; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; TC, total cholesterol.

Figure 1 Selection of two matched cohorts of patients on liraglutide (LIRA) or basal insulin supported oral therapy (BOT).

Demographic and clinical characteristics of the studied cohorts

Patient demographics and their clinical characteristics for the HbA_{1c} outcomes are shown in Table 1. The mean ages and gender distributions in the matched cohorts were similar (liraglutide cohort: 58.3 ± 10.3 years, 44% men; BOT cohort: 61.3 ± 10.5 years, 45% men).

At baseline, the cohorts were comparable in terms of HbA_{1c}, weight, BMI, and values of cardiovascular risk biomarkers; at initiation, 16% of the patients in the liraglutide cohort and 11% of the patients in the BOT cohort met their HbA_{1c} target. The mean BMI was 40.0 (±5.5) kg/m^2 in the liraglutide cohort and 37.7 (±4.4) kg/m^2 in the BOT cohort. Blood pressure and lipid values were also similar in the two cohorts. The median (IQR) time between baseline measurements and start of treatment was 31 (10-61) days for HbA_{1c} and 50 (22-110) days for BMI and weight. In both cohorts, the majority of patients were on statins and anti-hypertensives. Metformin combined with a sulphonylurea was the most often used antidiabetic treatment prior to the cohort entry date, at the cohort entry date and even after 12 months of treatment.

The median (IQR) duration of treatment with the studied drugs (matched cohorts) was 20.8 (10.8–34.5) months in the liraglutide cohort and 16.5 (9.5–29.5) months in the BOT cohort. The 50% attrition rate was reached earlier for the BOT cohort in the majority of analyses. Change in study drug (cessation or addition of any insulin or GLP-1RA therapy) was the most frequent reason for ending follow-up (liraglutide cohort, 61%; BOT cohort, 57%). Changes in OAD drug use were allowed and were similar between liraglutide and BOT (Table 1).

Table 1 Demographic, clinical and treatment characteristics of the unmatched and matched liraglutide and BOT cohorts at baseline and at 12 months of treatment for the main outcome, glycated haemoglobin

	Liraglutide		BOT	
	Unmatched n = 301	Matched n = 231	Unmatched n = 471	Matched n = 231
General characteristics				
Age (years), mean ± SD	57.5 ± 9.9	58.3 ± 10.3	62.5 ± 11.1	61.3 ± 10.5
Gender male, n (%)	156 (52)	101 (44)	164 (35)	104 (45)
Clinical parameters, mean ± SD*				
HbA_{1c} (mmol/mol)	68.4 ± 13.3	68.1 ± 13.8	70.1 ± 13.2	70.2 ± 12.8
On goal, n (%)	43 (14)	36 (16)	69 (15)	26 (11)
BMI (kg/m^2)	39.8 ± 5.5	40.0 ± 5.5	37.6 ± 4.2	37.7 ± 4.4
Weight (kg)	115.9 ± 17.8	115.4 ± 17.3	106.1 ± 16.5	107.7 ± 17.3
Systolic BP (mmHg)	137.9 ± 15.1	137.7 ± 15.5	138.7 ± 16.1	138.4 ± 16.3
Diastolic BP (mmHg)	80.6 ± 9.9	80.5 ± 10.1	80.1 ± 9.4	81.1 ± 9.5
TC (mmol/l)	4.4 ± 1.0	4.4 ± 1.0	4.6 ± 1.0	4.6 ± 1.0
LDL (mmol/l)	2.2 ± 0.8	2.3 ± 0.8	2.5 ± 0.9	2.5 ± 0.9
HDL (mmol/l)	1.06 ± 0.28	1.08 ± 0.29	1.12 ± 0.29	1.07 ± 0.29
Cardiovascular co-medication, n (%)				
Statins	222 (74)	169 (73)	345 (73)	168 (73)
Anti-hypertensives	244 (81)	184 (80)	388 (82)	198 (86)
Loop diuretics	38 (13)	29 (13)	75 (16)	32 (14)
Anticoagulants	106 (35)	79 (34)	175 (37)	91 (39)
Cardiac medication	26 (9)	20 (9)	53 (11)	23 (10)

	Liraglutide		BOT	
	Unmatched n = 301	Matched n = 231	Unmatched n = 471	Matched n = 231
Anti-diabetic treatment characteristics, n (%)				
OAD class prior to cohort entry date				
None	8 (3)	5 (2)	19 (4)	8 (3)
MET + SU	147 (49)	124 (54)	273 (58)	122 (53)
SU	30 (10)	22 (10)	48 (10)	22 (10)
MET	31 (10)	22 (10)	33 (7)	16 (7)
DPP-4i with SU and/or MET**	63 (21)	49 (21)	80 (17)	50 (22)
Other	22 (7)	9 (4)	18 (4)	13 (6)
Concomitant OAD class at cohort entry date				
None	24 (8)	15 (6)	35 (7)	15 (6)
MET + SU	135 (45)	126 (55)	258 (55)	126 (55)
SU	42 (14)	29 (13)	65 (14)	29 (13)
MET	76 (25)	54 (23)	84 (18)	54 (23)
DPP-4i with SU and/or MET**	11 (4)	5 (2)	22 (5)	5 (2)
Other	13 (4)	2 (1)	7 (1)	2 (1)
OAD class after 12 months				
None	21 (7)	14 (6)	22 (5)	12 (5)
MET + SU	88 (29)	69 (30)	156 (33)	77 (33)
SU	23 (8)	16 (7)	34 (7)	14 (6)
MET	71 (24)	60 (26)	74 (16)	47 (20)
DPP-4i with SU and/or MET**	3 (1)	1 (<0.5)	4 (1)	0 (0)
Other	9 (3)	4 (2)	3 (1)	0 (0)
<12 months of treatment	86 (29)	67 (29)	178 (38)	81 (35)
Duration of treatment with liraglutide or BOT (months)				
3 - <6	25 (8)	21 (9)	51 (11)	29 (13)
6 - <12	61 (20)	46 (20)	127 (27)	52 (23)
12 - <24	84 (28)	58 (25)	135 (29)	75 (32)
≥24	131 (44)	106 (46)	158 (34)	75 (32)
Median (IQR)	20.2 (10.8-34.5)	20.8 (10.8-34.5)	16.4 (9.4-30.6)	16.5 (9.5-29.5)
Reason end of observation				
Cessation of study drug	180 (60)	136 (59)	180 (38)	93 (40)
Add on of insulin/GLP-1RA	7 (2)	5 (2)	81 (17)	40 (17)
End of follow-up				
End of registration	0 (0)	0 (0)	9 (2)	6 (3)
Deceased	1 (<0.5)	0 (0)	8 (2)	3 (1)
End of study period	113 (38)	90 (39)	193 (41)	89 (39)

*Determined among patients with known value; **DPP-4i + SU + MET; DPP-4i + MET, DPP-4i + SU. Abbreviations: BOT, basal insulin supported oral therapy; BP, blood pressure; DPP-4i, dipeptidyl peptidase-4 (DPP-4) inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists; HbA_{1c}, haemoglobin A_{1c}; HDL, high density lipoprotein cholesterol, IQR, interquartile range; LDL, low density lipoprotein cholesterol; MET, metformin; OAD, oral anti-diabetics; SD, standard deviation; SU, sulfonylureas; TC, total cholesterol.

Clinical effectiveness

HbA_{1c} levels

Changes in HbA_{1c} from baseline at 3, 6, 9, and 12 months (LSM) are displayed in Table 2 and Figure 2. At 3 months, the mean decrease in HbA_{1c} (based on data from 231 patients in each cohort [100%]) was 10.0 mmol/mol in the liraglutide cohort and 3.8 mmol/mol in the BOT cohort; this statistically significant difference favoured liraglutide (-6.2 mmol/mol [95% CI: -8.3; -4.1], P < .0001 [Table 2]). At 6 and 9 months, the mean HbA_{1c} further decreased in both cohorts. At both time points, the differences remained significant in favour of liraglutide (-4.9 mmol/mol [95% CI: -6.9; -2.9] and -4.9 mmol/mol [95% CI: -7.1; -2.8], respectively; P < .0001 [Figure S1]).

At 12 months, with 72% (liraglutide) and 70% (BOT) of patients still being treated, the difference in HbA_{1c} from baseline was -12.2 mmol/mol in the liraglutide cohort and -8.8 mmol/mol in the BOT cohort (Table 2 and Figure 2). The difference between the two cohorts remained greater for liraglutide (-3.4 mmol/mol [95% CI: -5.8; -1.0]; P = .0053). These HbA_{1c} findings persisted at 15 months (the 50% attrition time point; Table S2 and Figure S2).

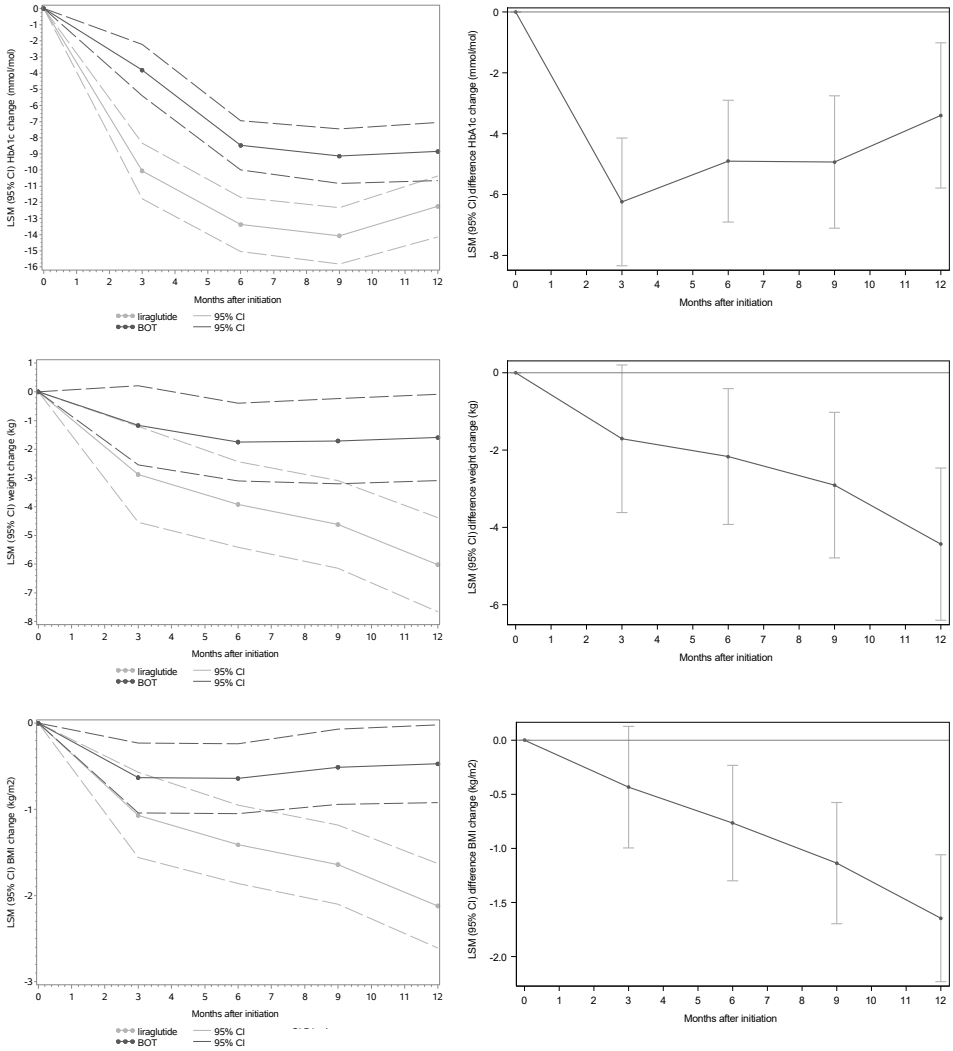
INDEX

Table 2 Least square mean changes from baseline in HbA_{1c} (mmol/mol), weight (kg), and BMI (kg/m^2) at 3, 6, 9, and 12 months after treatment initiation in the liraglutide and BOT cohorts

Months after initiation	Liraglutide		BOT		Liraglutide vs. BOT	
	n (%)	LSM change (95% CI)	n (%)	LSM change (95% CI)	LSM difference (95% CI)	p-value
HbA_{1c} (mmol/mol)						
0	231 (100)	0	231 (100)	0	0	-
3	231 (100)	-10.0 (-11.8; -8.3)	231 (100)	-3.8 (-5.4; -2.2)	-6.2 (-8.3; -4.1)	<0.0001
6	229 (99)	-13.4 (-15.0; -11.7)	229 (99)	-8.5 (-10.0; -6.9)	-4.9 (-6.9; -2.9)	<0.0001
9	188 (81)	-14.1 (-15.8; -12.3)	183 (79)	-9.1 (-10.8; -7.5)	-4.9 (-7.1; -2.8)	<0.0001
12	166 (72)	-12.2 (-14.1; -10.4)	161 (70)	-8.8 (-10.6; -7.0)	-3.4 (-5.8; -1.0)	0.0053
Weight (kg)						
0	81 (100)	0	81 (100)	0	0	-
3	81 (100)	-2.9 (-4.5; -1.2)	81 (100)	-1.2 (-2.6; 0.2)	-1.7 (-3.6; 0.2)	0.0802
6	80 (99)	-3.9 (-5.4; -2.4)	79 (98)	-1.8 (-3.1; -0.4)	-2.2 (-3.9; -0.4)	0.0160
9	72 (89)	-4.6 (-6.2; -3.1)	63 (78)	-1.7 (-3.2; -0.2)	-2.9 (-4.8; -1.0)	0.0026
12	60 (74)	-6.0 (-7.7; -4.4)	59 (73)	-1.6 (-3.1; -0.1)	-4.4 (-6.4; -2.5)	<0.0001
BMI (kg/m^2)						
0	83 (100)	0	83 (100)	0	0	-
3	83 (100)	-1.1 (-1.6; -0.6)	83 (100)	-0.6 (-1.0; -0.2)	-0.4 (-1.0; 0.1)	0.1311
6	82 (99)	-1.4 (-1.9; -1.0)	81 (98)	-0.6 (-1.0; -0.2)	-0.8 (-1.3; -0.2)	0.0051
9	74 (89)	-1.6 (-2.1; -1.2)	67 (81)	-0.5 (-0.9; -0.1)	-1.1 (-1.7; -0.6)	<0.0001
12	63 (76)	-2.1 (-2.6; -1.6)	57 (69)	-0.5 (-0.9; 0.0)	-1.6 (-2.2; -1.1)	<0.0001

Abbreviations: BMI, body mass index; BOT, basal insulin supported oral therapy; HbA_{1c}, haemoglobin A_{1c}; kg, kilograms; LSM, least square mean; 95% CI, 95% confidence interval.

The proportion of patients reaching their individual HbA_{1c} target in the liraglutide cohort and the BOT cohort increased from 16% and 11%, respectively, at baseline to 57% and 33%, respectively, at 3 months. At 12 months, the difference still existed, with 45% of the patients in the liraglutide cohort and 38% in the BOT cohort reaching their target HbA_{1c} (Table 3).



Abbreviations: BOT, basal insulin supported oral therapy; 95% CI, 95% confidence interval.

Figure 2 Least square mean (LSM) changes from baseline in glycated haemoglobin (HbA_{1c}, mmol/mol), weight (kg) and body mass index (BMI, kg/m^2) at 3, 6, 9 and 12 months after treatment initiation in the liraglutide and BOT cohorts.

Weight and BMI values

In the liraglutide cohort, mean weight declined over time, while a minimal decline was observed in the BOT cohort (Table 2 and Figure 2). The difference in weight change between the liraglutide cohort and the BOT cohort was statistically significant at 12 months (-6.0 vs -1.6 kg; P < .0001) and at 18 months (-5.3 vs -0.6 kg; P < .0001 [Table S2 and Figure S2]).

The mean change in BMI from baseline in the liraglutide cohort steadily decreased, reaching a mean reduction of -2.1 kg/m^2 at 12 months (Table 2 and Figure 2). In the BOT cohort, BMI declined by -0.6 kg/m^2 at 3 months with no change at subsequent time points. Consequently, the differences between the cohorts increased at each time point and reached significance at 6 (P = .0051), 9 and 12 months (P < .0001). These findings persisted at 15 months, the 50% attrition time point (Table S2 and Figure S2).

INDEX

Cardiovascular risk biomarkers

The mean changes from baseline and mean differences in change from baseline between cohorts for several cardiovascular risk biomarkers, including SBP, DBP, total cholesterol, HDL cholesterol and LDL cholesterol, are summarized in Table S3 and Figures S3 and S4. The trends over time for SBP and DBP in both cohorts fluctuated and were not significantly different between cohorts. In both cohorts, the lipid levels changed slightly over time with no statically significant differences between cohorts. For all cardiovascular biomarkers, the trends persisted at 15 months (Table S3 and Figures S3 and S4).

Table 3 Number and proportion (%) of patients reaching defined HbA_{1c} target (≤53 mmol/mol, ≤58 mmol/mol and ≤64 mmol/mol)* at 3, 6, 9, and 12 months after treatment initiation for the unmatched and matched cohorts treated with liraglutide or BOT

	Unmatched liraglutide		Matched liraglutide		Unmatched BOT		Matched BOT	
Months after initiation	n**	n (%) at goal	n**	n (%) at goal	n**	n (%) at goal	n**	n (%) at goal
0	301	43 (14)	231	36 (16)	471	69 (15)	231	26 (11)
3	280	144 (51)	214	123 (57)	429	167 (39)	206	68 (33)
6	194	97 (50)	151	78 (52)	262	112 (43)	131	45 (34)
9	132	67 (51)	106	57 (54)	161	71 (44)	76	29 (38)
12	83	38 (46)	64	29 (45)	95	46 (48)	45	17 (38)

*HbA_{1c} targets were ≤53 mmol/mol (≤7.0%) for patients aged <70 years, ≤58 mmol/mol (≤7.5%) for older patients with a diabetes duration <10 years, and ≤64 mmol/mol (≤8.0%) for all remaining patients. **Patients still on treatment during interval. Abbreviations: BOT, basal insulin supported oral therapy; HbA_{1c}, haemoglobin A1c.

Discussion

The results of the present study show that initiating liraglutide, compared with BOT, in a real-world setting is associated with significant reductions in HbA_{1c} and weight in obese patients with T2DM. Initiating treatment with liraglutide led to optimization of glycaemic control and

weight reductions after 3 and 6 months. At 12 months, the differences in HbA_{1c} and weight for liraglutide vs those for BOT were 3.4 mmol/mol and 4.4 kg, respectively. These findings are consistent with clinical evidence from several RCTs[23] and real-world observational studies previously reported for liraglutide.[24]

To our knowledge, this study comparing the effectiveness of liraglutide and BOT in two propensity score-matched T2DM cohorts of obese patients is the first of its kind. Only in the early pilot phase of the INITIATOR study was a real-world comparison made between liraglutide and insulin glargine in a cohort of patients with T2DM.[25] That study showed no difference in HbA_{1c} between liraglutide and insulin glargine (weight was not captured) after 9 months of treatment. However, matching was not applied, resulting in significant baseline differences between the study groups.[25] In the current study, 70 patients were lost in the primary outcome analysis due to a lack of overlap in matching criteria, indicating that the liraglutide and BOT populations were indeed very different, and matching was imperative for comparison between cohorts.

Nearly 50% of the patients on liraglutide maintained the HbA_{1c} goal levels at 12 months. This sustained optimization of the HbA_{1c} levels was accompanied by a significant decrease in the BMI values towards the end of the first year after treatment initiation. These results are in line with other similar long-term findings from clinical and real-world studies, showing that liraglutide therapy provides sustained glycaemic control and significant weight loss in patients with T2DM; these two beneficial effects seem to be more pronounced with liraglutide than with other GLP-1RAs.[24,26] It should also be mentioned that weight changes on the order of a 5% loss lead to decreased insulin resistance and improved glycaemic levels.[23]

In the present real-world study, small changes in cardiovascular risk biomarkers, such as blood pressure or lipids, were found, with non-significant differences between patients on liraglutide and BOT. The observed mean changes vs baseline for SBP fluctuated over time but were very small, in line with the results from clinical trials. For example, data from a pooled analysis of six RCTs showed a rapid and consistent change in SBP with 1.2 mg liraglutide (-2.7 mmHg vs baseline after 26 weeks),[27] while in the present real-world study, the mean change in SBP was -1.2 mmHg at 6 months. Although seemingly small and non-significant, the changes in lipids (particularly LDL cholesterol) observed in the present study are in line with the data from RCTs showing that liraglutide significantly improves the levels of total cholesterol, LDL cholesterol, free fatty acids, and triglycerides to a small extent.[23] Data from the LEADER trial show that treatment with liraglutide leads to a significant reduction in cardiovascular risk in patients with T2DM and a high risk for cardiovascular events.[27]

Early evidence from the United Kingdom Prospective Diabetes Study found that a 1% decrease in mean HbA_{1c} (i.e., 11 mmol/mol) was associated with a statistically significant risk reduction for heart failure, myocardial infarction (MI) and stroke.[28] More recent data from population-based studies also showed that achievement of desirable HbA_{1c} levels within 6 months of treatment initiation or adjustment was associated with a lower risk of myocardial infarction or stroke and death in patients with T2DM.[29] Another cohort study conducted in obese patients with T2DM from the UK showed that adding a GLP-1RA was associated with

INDEX

a greater decrease in the risk of major adverse cardiovascular events than adding insulin therapy as the third glucose-lowering agent.[30]

Furthermore, decreasing cardiovascular risk, reducing weight and avoiding hypoglycaemia are the attributes of treatments that are most valued by people with T2DM.[31] These aspects are of crucial importance in treatment decision-making because their consideration may improve adherence and persistence, which are both needed to achieve the expected clinical benefits.[32]

The results of the present study should be interpreted in the context of several limitations. First, the study is based on data from a Dutch population sample, therefore, the findings may not be representative of inhabitants of other countries, especially taking into account the specific Dutch reimbursement restrictions (mandatory specialist prescribing, failed oral alternatives, BMI ≥35 kg/m^2). Second, information on patients' T2DM history, hypoglycaemia, heart rate, comorbidities, changes in OAD co-medications, and other factors that may determine the response to treatments were not accounted for during follow-up or at the end the of study (Table 1). In addition, in this real-world study, possible side effects of the therapies could not be evaluated. Databases such as the PHARMO Database Network do not provide the level of clinical detail that is available in secondary care outpatient medical records. The information available on the patients eligible for this study was therefore restricted to the type of data provided in the database. Third, database studies can establish only associations and not cause-and-effect relationships, although inferential analyses were performed. Fourth, propensity score matching is a well-recognized statistical technique that allows the design and analysis of real-world studies while mimicking some of the characteristics of an RCT. The propensity score is a balancing score: conditional on this score, the distribution of observed baseline characteristics will be similar between treated and untreated patients, for instance.[33] Sample matching based on propensity scores, however, has some limitations. The number of subjects in the matched final sample might be reduced substantially, and this possibility should be balanced with the need to maintain statistical power. Another drawback is that two completely unrelated factors in the model may result in a similar propensity score. Additionally, a correlation between factors in the propensity score model may have the undesired effect that differences between less predictive characteristics may actually increase. In the present study, the varying strengths of the associations of variables in the propensity model sometimes augmented differences in characteristics that were less predictive for receiving GLP-1RA (e.g., weight was much stronger than age, but age was associated with weight). Further refinement of the matching procedures to reduce these differences resulted in fewer matched patients and thus a lack of power; therefore, these remaining differences in variable distributions were permitted and further adjusted for in the comparative analyses models. Finally, it was assumed that patients took their medicines as dispensed and followed medical recommendations on dosing and frequency. The effect of poor adherence to treatments was not evaluated, which may have affected the outcome measures.

Nevertheless, the study relied on an updated, large and comprehensive database and used a mixed model that allowed longitudinal follow-up despite intervals with missing outcome

information. Observational studies complement clinical trials and provide a valuable research tool for assessing the effectiveness of treatments because these studies account for clinical practice variability and patient diversity in a real-world setting. Results such as those obtained in this study could be a relevant and useful source of information for clinicians and payers when updating current clinical guidelines, which require consideration of real-world evidence and the multifactorial nature of diabetes. The availability of real-world data in the PHARMO Database Network and other databases also opens up opportunities for further studies, including those with a longer follow-up time, and the potential to link clinical outcomes with direct healthcare resource use.

In conclusion, the present real-world evidence study is the first to demonstrate the clinical effectiveness of adding liraglutide vs BOT to existing OAD therapy in two matched cohorts of obese people with T2DM. The results confirmed that intensification with liraglutide was associated with a significant reduction in HbA_{1c} levels compared with those with BOT over a period of 12 months after treatment initiation. In addition, compared with BOT treatment, treatment with liraglutide also led to significant weight and BMI reductions over time. In both cohorts, the fluctuations in SBP, DBP, and lipids were small, and no differences were observed between the cohorts. The results of this study confirm previously reported clinical findings from RCTs of liraglutide. This study provides important insights on the long-term clinical effectiveness of initiating liraglutide vs BOT in obese people with T2DM in a real-world setting.

INDEX

Acknowledgements

The authors thank all the healthcare providers that contributed information to the PHARMO Database Network. The authors also thank Silvia Paz Ruiz MD MMedSci (Terminal 4 Communications) for providing medical writing support, proofreading, and editing in accordance with the Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Conflict of interest

J.A.O., E.M.H., F.J.A.P., and R.M.C.H. are employees of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities, as well as for several pharmaceutical companies. E.L.H. and A.W.D. are employees of Novo Nordisk. C.K.T. is an employee of Novo Nordisk and owns stocks in Novo Nordisk A/S.

References

1. Tamayo T, Rosenbauer J, Wild SH, et al. Diabetes in Europe: an update. **Diabetes Res Clin Pract**. 2014;2:206-217.
2. van Dieren S, Beulens JW, van der Schouw YT, et al. The global burden of diabetes and its complications: an emerging pandemic. **Eur J Cardiovasc Prev Rehabil**. 2010;S3-8.
3. Eeg-Olofsson K, Cederholm J, Nilsson PM, et al. Risk of cardiovascular disease and mortality in overweight and obese patients with type 2 diabetes: an observational study in 13,087 patients. **Diabetologia**. 2009;1:65-73.
4. Liu XM, Liu YJ, Zhan J, et al. Overweight, obesity and risk of all-cause and cardiovascular mortality in patients with type 2 diabetes mellitus: a dose-response meta-analysis of prospective cohort studies. **Eur J Epidemiol**. 2015;1:35-45.
5. Summers RH, Moore M, Byrne J, et al. Perceptions of weight, diabetes and willingness to participate in randomised controlled trials of bariatric surgery for patients with type 2 diabetes mellitus and body mass index 30-39.9 kg/m(2). **Obes Surg**. 2015;6:1039-1046.
6. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. **Diabetes Care**. 2013;4:1033-1046.
7. Dimitrova M, Doneva M, Valov V, et al. Cost of hospitalizations due to microvascular and macrovascular complications in type 1 and type 2 diabetic patients in Bulgaria. **Biotechnology & Biotechnological Equipment**. 2015;4:805-813.
8. Domeikiene A, Vaivadaite J, Ivanauskiene R, et al. Direct cost of patients with type 2 diabetes mellitus healthcare and its complications in Lithuania. **Medicina (Kaunas)**. 2014;1:54-60.
9. Peters ML, Huisman EL, Schoonen M, et al. The current total economic burden of diabetes mellitus in the Netherlands. **Neth J Med**. 2017;7:281-297.
10. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). **Diabetologia**. 2012;6:1577-1596.
11. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. **Diabetologia**. 2015;3:429-442.
12. Han TS, Lean ME. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease. **JRSM Cardiovasc Dis**. 2016;2048004016633371.
13. Yandrapalli S, Aronow WS. Cardiovascular benefits of the newer medications for treating type 2 diabetes mellitus. **J Thorac Dis**. 2017;7:2124-2134.
14. Marrett E, Stargardt T, Mavros P, et al. Patient-reported outcomes in a survey of patients treated with oral antihyperglycaemic medications: associations with hypoglycaemia and weight gain. **Diabetes Obes Metab**. 2009;12:1138-1144.

15. Martyn-Nemeth P, Schwarz Farabi S, Mihailescu D, et al. Fear of hypoglycemia in adults with type 1 diabetes: impact of therapeutic advances and strategies for prevention - a review. **J Diabetes Complications**. 2016;1:167-177.
16. Monami M, Dicembrini I, Kundisova L, et al. A meta-analysis of the hypoglycaemic risk in randomized controlled trials with sulphonylureas in patients with type 2 diabetes. **Diabetes Obes Metab**. 2014;9:833-840.
17. Abd El Aziz MS, Kahle M, Meier JJ, et al. A meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head studies in type 2 diabetic patients. **Diabetes Obes Metab**. 2017;2:216-227.
18. Fadini GP, Zatti G, Consoli A, et al. Rationale and design of the DARWIN-T2D (DApagliflozin Real World evIdeNce in Type 2 Diabetes): A multicenter retrospective nationwide Italian study and crowdsourcing opportunity. **Nutr Metab Cardiovasc Dis**. 2017;12:1089-1097.
19. PHARMO Institute for Drug Outcomes. www.pharmo.nl. Accessed November, 2017.
20. Rutten GEHM, De Grauw WJC, Nijpels G, et al. NHG-Standaard Diabetes mellitus type 2 (Derde herziening). **Huisarts Wet**. 2013;10:512-525.
21. Klein S, Sheard NF, Pi-Sunyer X, et al. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies. A statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. **Am J Clin Nutr**. 2004;2:257-263.
22. Ashbeck EL, Bell ML. Single time point comparisons in longitudinal randomized controlled trials: power and bias in the presence of missing data. **BMC Med Res Methodol**. 2016;43.
23. Rigato M, Fadini GP. Comparative effectiveness of liraglutide in the treatment of type 2 diabetes. **Diabetes Metab Syndr Obes**. 2014;107-120.
24. Ostawal A, Mocevic E, Kragh N, et al. Clinical Effectiveness of Liraglutide in Type 2 Diabetes Treatment in the Real-World Setting: A Systematic Literature Review. **Diabetes Ther**. 2016;3:411-438.
25. Thayer S, Wei W, Buysman E, et al. The INITIATOR study: pilot data on real-world clinical and economic outcomes in US patients with type 2 diabetes initiating injectable therapy. **Adv Ther**. 2013;12:1128-1140.
26. Trujillo JM, Nuffer W, Ellis SL. GLP-1 receptor agonists: a review of head-to-head clinical studies. **Ther Adv Endocrinol Metab**. 2015;1:19-28.
27. Fonseca VA, Devries JH, Henry RR, et al. Reductions in systolic blood pressure with liraglutide in patients with type 2 diabetes: insights from a patient-level pooled analysis of six randomized clinical trials. **J Diabetes Complications**. 2014;3:399-405.
28. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. **BMJ**. 2000;7258:405-412.

29. Svensson E, Baggesen LM, Johnsen SP, et al. Early Glycemic Control and Magnitude of HbA1c Reduction Predict Cardiovascular Events and Mortality: Population-Based Cohort Study of 24,752 Metformin Initiators. **Diabetes Care**. 2017;6:800-807.
30. Anyanwagu U, Mamza J, Mehta R, et al. Cardiovascular events and all-cause mortality with insulin versus glucagon-like peptide-1 analogue in type 2 diabetes. **Heart**. 2016;19:1581-1587.
31. Morillas C, Feliciano R, Catalina PF, et al. Patients' and physicians' preferences for type 2 diabetes mellitus treatments in Spain and Portugal: a discrete choice experiment. **Patient Prefer Adherence**. 2015;1443-1458.
32. Buysman EK, Liu F, Hammer M, et al. Impact of medication adherence and persistence on clinical and economic outcomes in patients with type 2 diabetes treated with liraglutide: a retrospective cohort study. **Adv Ther.** 2015;4:341-355.
33. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. **Multivariate Behav Res**. 2011;3:399-424.

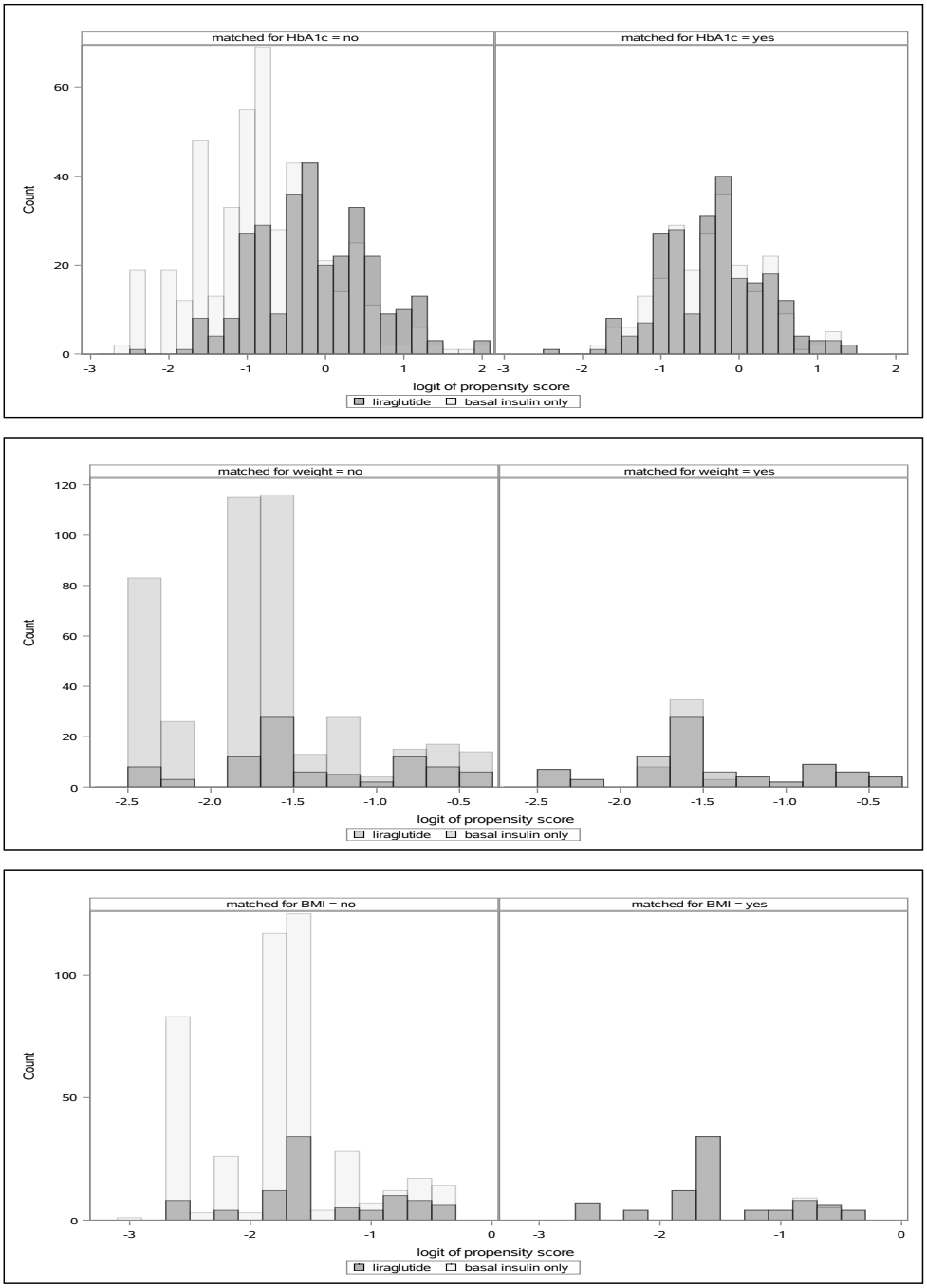
INDEX

Supporting Information

Table S1 Variables and the corresponding categories applied in the propensity score to calculate the probability of receiving liraglutide

Variables	Categories
Number of OAD classes in the entire available history	1, 2, 3, ≥4
Duration of OAD treatment in the entire available history defined as the time between first OAD and cohort entry date (years)	<2, 2-<4, 4-<6, 6-<8, ≥8
Type of OAD treatment prior to starting liraglutide or BOT	None, mono therapy, dual therapy, multiple therapy
OAD treatment prior to starting liraglutide or BOT	None, SU, metformin, metformin + SU, DPP-4i + metformin, DPP-4i + SU, DPP-4i + SU + metformin, SU + TZD + metformin, other
Year of cohort entry date	2010-2011, 2012-2015
HbA_{1c} (mmol/mol)	<58, 58-<69, ≥69, missing
Weight*(kg)	<125, ≥125, missing
CKD stage	Stage 1, 2, 3, 4, 5, missing
Age (years)	<50, 50-<60, 60-<70, ≥70
Gender	Female, male
Systolic BP* (mmHg)	<140, ≥140, missing
Diastolic BP* (mmHg)	<90, ≥90, missing
TC (mmol/L)	<4.5, ≥4.5, unknown
LDL (mmol/L)	<2.5, ≥2.5, unknown
HDL (mmol/L)	<1.0, ≥1.0, unknown
Cardiovascular co-medication use in the year prior to cohort entry date	Statins, anti-hypertensives, loop diuretics, anticoagulants, cardiac therapy

*For the outcomes HbA_{1c} and lipids, BP and weight were not included in the propensity score. Abbreviations: BOT, basal insulin supported oral therapy; BP, blood pressure; CKD, chronic kidney disease; DPP-4i, dipeptidyl peptidase-4 (DPP-4) inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists; HbA_{1c}, haemoglobin A_{1c}; HDL, high density lipoprotein cholesterol; MET, metformin; LDL, low density lipoprotein cholesterol; OAD, oral anti-diabetics; SU, sulfonylureas; TC, total cholesterol; TZD, thiazolidinediones.



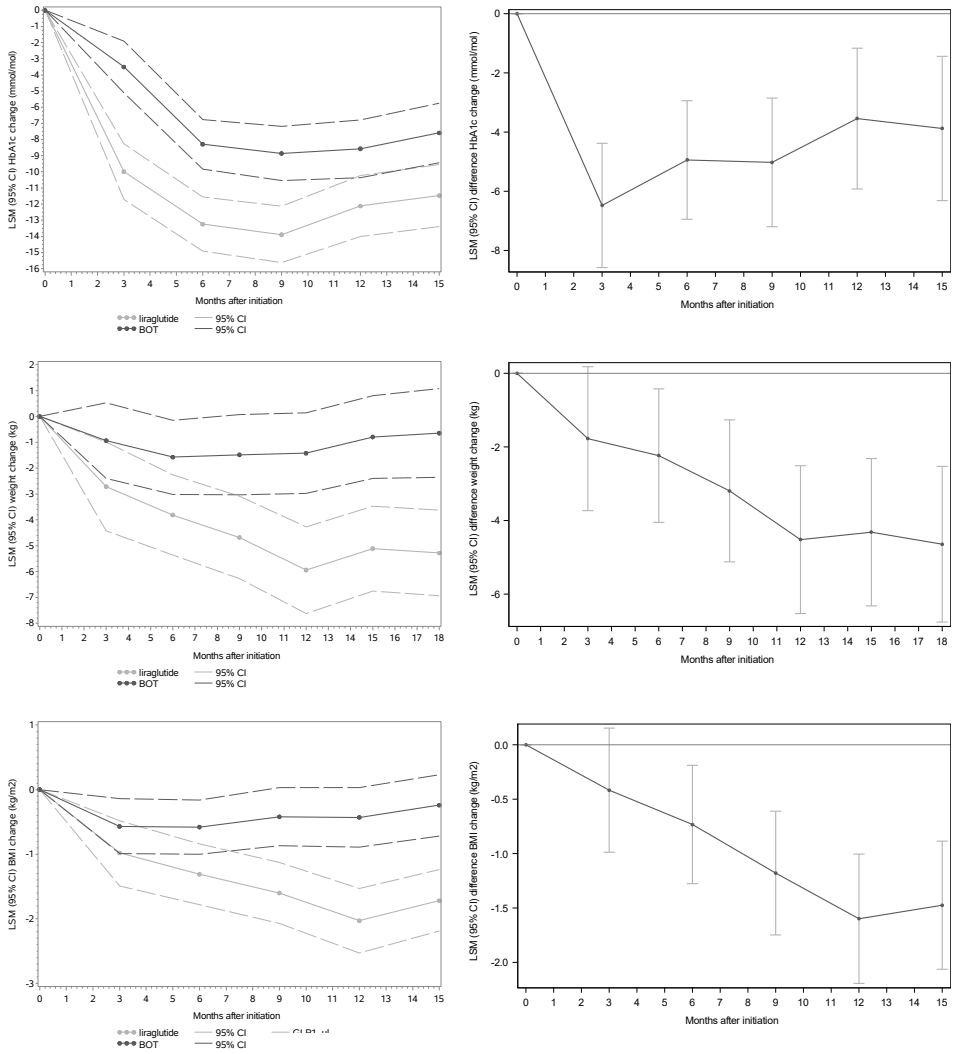
Abbreviations: BMI, body mass index; BOT, basal insulin supported oral therapy; HbA_{1c}, haemoglobin A_{1c}.

Figure S1 Logit of propensity score distribution prior to and after matching for HbA_{1c}, for BMI and for weight.

Table S2 Least square mean changes from baseline and least square mean differences for HbA_{1c} (mmol

Months after initiation	Liraglutide		BOT		Liraglutide vs. BOT	
	n (%)	LSM change (95% CI)	n (%)	LSM change (95% CI)	LSM difference (95% CI)	p-value
HbA_{1c} (mmol/mol)						
0	231 (100)	0	231 (100)	0	0	-
15	143 (62)	-11.5 (-13.4; -9.5)	135 (58)	-7.6 (-9.4; -5.7)	-3.9 (-6.3; -1.4)	0.0018
Weight (kg)						
0	83 (100)	0	83 (100)	0	0	-
15	54 (67)	-5.1 (-6.7; -3.5)	49 (60)	-0.8 (-2.4; 0.8)	-4.3 (-6.3; -2.3)	<0.0001
18	47 (58)	-5.3 (-6.9; -3.6)	42 (52)	-0.6 (-2.4; 1.1)	-4.6 (-6.8; -2.5)	<0.0001
BMI (kg/m^2)						
0	83 (100)	0	83 (100)	0	0	-
15	57 (69)	-1.7 (-2.2; -1.2)	46 (55)	-0.2 (-0.7; 0.2)	-1.5 (-2.1; -0.9)	<0.0001

Abbreviations: BOT, basal insulin supported oral therapy; BMI, body mass index; HbA_{1c}, haemoglobin A_{1c}; LSM, least square mean; 95% CI, 95% confidence interval.



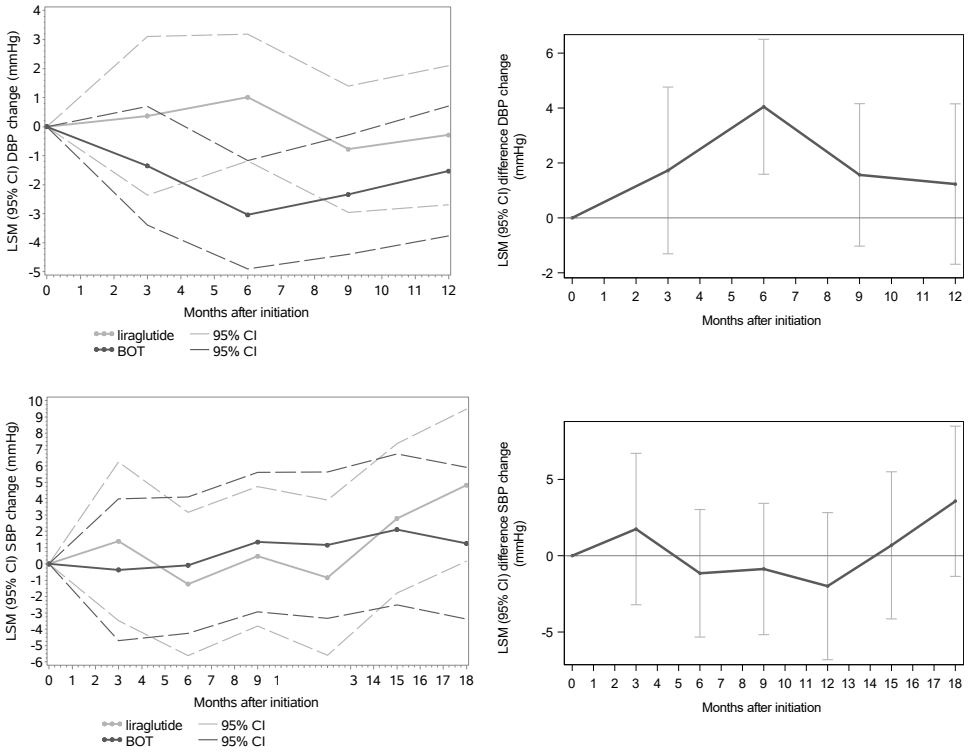
Abbreviations: BOT, basal insulin supported oral therapy; 95% CI, 95% confidence interval.

Figure S2 Least square means (LSM) changes from baseline in glycated haemoglobin (HbA_{1c}, mmol/mol), weight (kg), and body mass index (BMI, kg/m^2) at 3, 6, 9, and 12 months and at the ≥50% attrition time point after treatment initiation in the liraglutide and BOT cohorts.

Table S3 Least square mean changes from baseline and least square mean differences in cardiovascular risk biomarkers at 3, 6, 9, 12, 15, and 18 months (≥50% attrition) after treatment initiation in the liraglutide and the basal insulin only cohorts

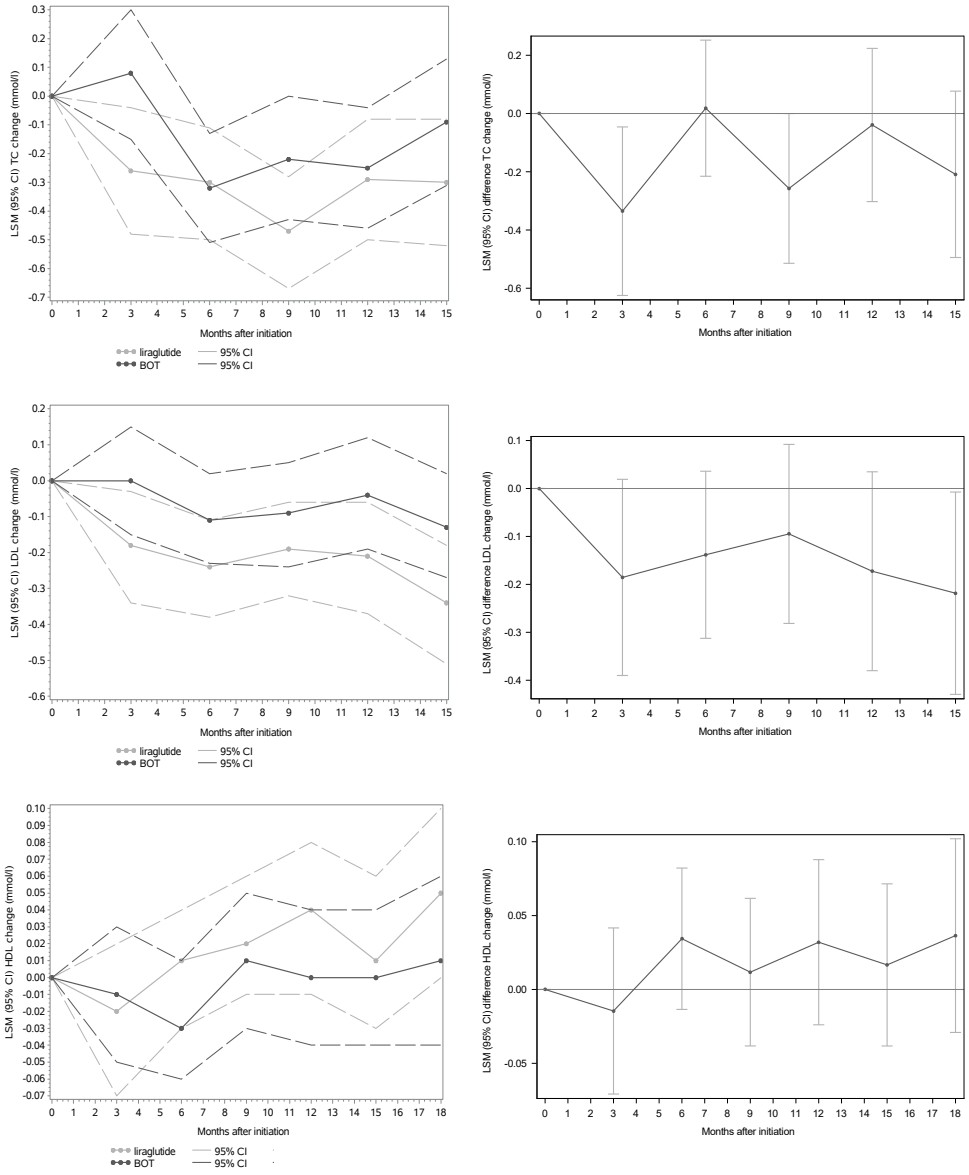
Months after initiation	Liraglutide		BOT		Liraglutide vs. BOT	
	n (%)	LSM change (95% CI)	n (%)	LSM change (95% CI)	LSM difference (95% CI)	p-value
Systolic BP (mmHg)						
0	98 (100)	0	98 (100)	0	0	-
3	98 (100)	1.5 (-3.2; 6.2)	98 (100)	-0.4 (-4.6; 3.9)	1.9 (-2.9; 6.6)	0.4439
6	98 (100)	-1.2 (-5.5; 3.1)	96 (98)	-0.4 (-4.4; 3.7)	-0.8 (-4.8; 3.2)	0.6869
9	87 (89)	0.1 (-4.0; 4.3)	81 (83)	0.9 (-3.3; 5.1)	-0.8 (-4.9; 3.4)	0.7162
12	68 (69)	-1.2 (-5.8; 3.5)	69 (70)	0.7 (-3.7; 5.1)	-1.9 (-6.5; 2.8)	0.4259
15	61 (62)	2.8 (-1.8; 7.4)	58 (59)	2.1 (-2.5; 6.7)	0.7 (-4.1; 5.5)	0.7822
18	53 (54)	4.8 (0.2; 9.5)	53 (54)	1.3 (-3.4; 5.9)	3.6 (-1.4; 8.5)	0.1558
Diastolic BP (mmHg)						
0	93 (100)	0	93 (100)	0	0	-
3	93 (100)	0.4 (-2.4; 3.1)	93 (100)	-1.4 (-3.4; 0.7)	1.7 (-1.3; 4.8)	0.2651
6	93 (100)	1.0 (-1.2; 3.2)	90 (97)	-3.0 (-4.9; -1.2)	4.0 (1.6; 6.5)	0.0013
9	82 (88)	-0.8 (-3.0; 1.4)	71 (76)	-2.3 (-4.4; -0.3)	1.6 (-1.0; 4.2)	0.2374
12*	65 (70)	-0.3 (-2.7; 2.1)	60 (65)	-1.5 (-3.8; 0.7)	1.2 (-1.7; 4.2)	0.4086
TC (mmol/L)						
0	154 (100)	0	154 (100)	0	0	-
3	154 (100)	-0.3 (-0.5; 0.0)	154 (100)	0.1 (-0.1; 0.3)	-0.3 (-0.6; -0.0)	0.0221
6	153 (99)	-0.3 (-0.5; -0.1)	151 (98)	-0.3 (-0.5; -0.1)	0.0 (-0.2; 0.3)	0.7837
9	132 (86)	-0.5 (-0.7; -0.3)	121 (79)	-0.2 (-0.4; 0.0)	-0.2 (-0.5; 0.0)	0.0538
12	111 (72)	-0.3 (-0.5; -0.1)	105 (68)	-0.3 (-0.5; -0.1)	-0.0 (-0.3; 0.2)	0.8520
15	94 (61)	-0.3 (-0.5; -0.1)	90 (58)	-0.1 (-0.3; 0.1)	-0.2 (-0.5; 0.1)	0.1523
LDL (mmol/L)						
0	160 (100)	0	160 (100)	0	0	-
3	160 (100)	-0.2 (-0.3; 0.0)	160 (100)	0.0 (-0.1; 0.2)	-0.2 (-0.4; 0.0)	0.0831
6	159 (99)	-0.2 (-0.4; -0.1)	159 (99)	-0.1 (-0.2; 0.0)	-0.1 (-0.3; 0.0)	0.1481
9	136 (85)	-0.2 (-0.3; 0.0)	128 (80)	-0.1 (-0.2; 0.1)	-0.1 (-0.3; 0.1)	0.3114
12	110 (69)	-0.2 (-0.3; 0.0)	108 (68)	0.0 (-0.2; 0.1)	-0.2 (-0.4; 0.0)	0.1053
15	95 (59)	-0.3 (-0.5; -0.2)	91 (57)	-0.1 (-0.3; 0.0)	-0.2 (-0.4; -0.0)	0.0428
HDL (mmol/L)						
0	163 (100)	0	163 (100)	0	0	-
3	163 (100)	-0.02 (-0.06; 0.02)	163 (100)	-0.01 (-0.05; 0.03)	-0.01 (-0.07; 0.04)	0.6626
6	162 (99)	0.01 (-0.03; 0.04)	162 (99)	-0.03 (-0.06; 0.01)	0.03 (-0.01; 0.08)	0.1387
9	137 (84)	0.02 (-0.01; 0.05)	135 (83)	0.01 (-0.03; 0.04)	0.01 (-0.03; 0.06)	0.5622
12	116 (71)	0.04 (0.00; 0.08)	118 (72)	0.00 (-0.04; 0.04)	0.04 (-0.02; 0.09)	0.1676
15	100 (61)	0.01 (-0.03; 0.06)	104 (64)	0.00 (-0.04; 0.04)	0.02 (-0.04; 0.07)	0.5527
18	87 (53)	0.05 (0.00; 0.10)	86 (53)	0.01 (-0.04; 0.06)	0.04 (-0.03; 0.10)	0.2760

*≥50% attrition time point was 12 months for diastolic BP. Abbreviations: BOT: basal insulin supported oral therapy; BP, blood pressure; HDL, high density lipoprotein cholesterol; LDL: low density lipoprotein cholesterol; LSM: least square mean; TC: total cholesterol; 95% CI: 95% confidence interval.



Abbreviations: BOT, basal insulin supported oral therapy; 95% CI, 95% confidence interval.

Figure S3 Least square means (LSM) changes from baseline in systolic and diastolic blood pressure (mmHg) at 3, 6, 9, and 12 months and at the ≥50% attrition time point after treatment initiation in the liraglutide and BOT cohorts.



Abbreviations: BOT, basal insulin supported oral therapy; 95% CI, 95% confidence interval.

Figure S4 Least square means (LSM) changes from baseline in total cholesterol (TC, mmol/L), low density lipoprotein cholesterol (LDL, mmol/L) and high density lipoprotein cholesterol (HDL, mmol/L) at 3, 6, 9, and 12 months and at the ≥50% attrition time point after treatment initiation in the liraglutide and BOT cohorts.

CHAPTER 5

Relationship between different measures of glycaemic exposure and microvascular and macrovascular complications in patients with type 2 diabetes mellitus: an observational cohort study

Rients P.T. van Wijngaarden, Jetty A. Overbeek, Edith M. Heintjes, Agata Schubert, Joris Diels, Huub Straatman, Ewout W. Steyerberg, Ron M.C. Herings

Diabetes Ther. 2017 Oct;8(5):1097-1109. doi: 10.1007/s13300-017-0301-4

Abstract

Introduction: This retrospective cohort study investigated the relation between different measures of glycaemic exposure and micro- and macrovascular complications among patients with type 2 diabetes.

Methods: The analysis included patients receiving oral antihyperglycaemic agents between 1 January 2006 and 31 December 2014 from the General Practitioner Database from the PHARMO Database Network. All recorded HbA_{1c} levels during follow-up were used to express glycaemic exposure in four ways: index HbA_{1c}, time-dependent HbA_{1c}, exponential moving average (EMA) and glycaemic burden. Association between glycaemic exposure and micro-/macrovascular complications was analysed by estimating hazard ratios and 95% confidence intervals using an adjusted (time-dependent) Cox proportional hazards model.

Results: The analysis included 32,725 patients (median age, 65 years; 47% female). Median follow-up was 5.4 years; median number of HbA_{1c} measurements per patient was 18.0. From all measures, HbA_{1c} at index showed the weakest relation between all micro-/macrovascular complications, with coronary artery disease (CAD) having the highest HR (95% CI): 1.18 (1.04-1.34) for HbA_{1c} ≥64 mmol/mol (8%). The time-dependent HbA_{1c} model showed a significant association only for microvascular complications, with retinopathy having the highest HR (95% CI): 1.55 (1.40-1.73) for HbA_{1c} ≥64 mmol/mol (8%). EMA-defined exposure showed similar findings, although the effect of retinopathy was more pronounced [HR (95% CI): 1.81 (1.63-2.02) for HbA_{1c} ≥64 mmol/mol (8%)] and was also predictive for CAD [HR (95% CI): 1.29 (1.10-1.50) for HbA_{1c} ≥64 mmol/mol (8%)]. A statistically significant relation with glycaemic burden was found for all selected micro-/macrovascular complications, with retinopathy having the highest HR (95% CI): 2.60 (2.19-3.07) for glycaemic burden years >3.

Conclusion: This study shows that greater and more prolonged exposure to hyperglycaemia increases the risk of micro- and macrovascular complications.
Funding: Janssen Pharmaceutica NV.

INDEX

Introduction

Type 2 diabetes mellitus (T2DM) is a complex disease with many associated long-term complications and a major impact on the daily lives of patients. High glycaemia shows a positive correlation with both micro- and macrovascular complications.[1-3] Therefore, to prevent or slow these complications, good glycaemic control is thought to be important.[4] In general practice, glycosylated haemoglobin (HbA_{1c}) is often used as a measure of glycaemic control. The advantage of using HbA_{1c} opposed to blood glucose level is that is measures the average plasma glucose level over a period of 2-3 months.[5] The HbA_{1c} target is generally 53 mmol/mol (7%),[6] nevertheless, T2DM patients often do not reach the recommended glycaemic target and stay uncontrolled for long periods of time.[7]

When assessing the risk associated with high glycaemia, HbA_{1c} measurements are often evaluated at a single point in time, which can lead to an underestimation of the role of HbA_{1c} as a risk factor,[8,9] as it does not take the level of glycaemic control over time into account. An updated mean HbA_{1c} is sometimes used instead of the single measure as a more appropriate approximation of glycaemic exposure as it is calculated as the average of all previous measurements and is recalculated if new measurements are added.[1] Using an UM has been shown to have greater predictive power;[1,10] however, while an UM does reflect the level of hyperglycaemia over time, irregular intervals between measurements may have a significant impact. Infrequent measurements during high glycaemic levels, mixed with frequent measurements during low glycaemic levels, may lead to underestimation of the glycaemic exposure over time and vice versa. The UM does not distinguish between recent and historic hyperglycaemic periods. To allow recent glycaemic levels to have more impact, more weight can be assigned to recent measurements in the UM [i.e., exponential moving average (EMA)]. However, this might also lead to diminished impact of historic periods of hyperglycaemia. By calculating an area under the curve (AUC) of glycaemic exposure, the effect of all measurements is taken into account, independent of whether the measurement is recent or in the past, but taking into account the duration of hyperglycaemic periods as well as the extent of the hyperglycaemia. This is referred to as glycaemic memory.[11-13]

The objective of this study is to investigate the relation between glycaemic exposure and micro- and macrovascular complications among patients with T2DM using real-world data. To further investigate the effect of changes in HbA_{1c} on long-term outcomes, different measures of glycaemic exposure are used, including single point measurements, EMA and AUC.

Methods

Setting

For this observational cohort study, data were obtained from the PHARMO Database Network. This population-based network of Dutch electronic healthcare databases combines rich, patient-centric data from different primary and secondary healthcare settings. Data from

INDEX

the General Practitioner (GP) Database were used, which cover approximately 2.5 million patients from 2005 to 2014. The GP Database comprises data from electronic patient records registered by GPs. The health records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. The prescription records include information on the type of product, prescription date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System. Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC), which can be mapped to ICD codes, but can also be entered as free text. The study period was defined as 1 January 2006-31 December 2014.

Patient Involvement

As this was an observational study using retrospective data, patients were not involved in the study design or conduct.

Study population

To investigate the relation between multiple measures of glycaemic exposure and macro- and microvascular complications, it was important to have regularly recorded HbA_{1c} measurements. Diabetes care in the Netherlands is mainly managed in the primary care setting and guided by the Dutch General Practitioner guideline for T2DM.[14] It is well organized, including regular check-ups. For our study, only general practices adhering to these regular check-ups were selected, which was defined as having at least 50% of its T2DM patients with at least three HbA_{1c} measurements per year. This selection was done at the practice level instead of patient level to avoid biased selection, as well-managed patients with T2DM may be monitored less frequently.

Within the selected practices, T2DM patients were identified as having either a diagnosis code (ICPC T90.02) or at least two consecutive prescriptions of oral antihyperglycaemic agents (AHA; ATC code A10B) within a 6-month period at any time in the available medication records. The index date was defined as the first oral AHA prescription after at least 1 year of enrolment. Patients without any oral AHA prescriptions during the study period were excluded as well as patients with diagnoses for T1DM, gestational diabetes or polycystic ovary syndrome (PCOS). Only patients between 40 and 84 years of age at the index date were included. The most recent HbA_{1c} measurement within one year prior to or at the index date was defined as the index HbA_{1c} measurement. If an index HbA_{1c} measurement was not available, the patient was excluded. Further exclusions were based on the event of interest. Patients with a prior event were excluded for the analysis of that specific event but were possibly included in other analyses. Finally, patients were required to have at least one HbA_{1c} measurement during follow-up. Again, this could differ per event of interest, since the end of follow up was determined as either the first occurrence of an event, death, loss to follow-up in the PHARMO Database Network or end of study period, whichever occurred first.

The following characteristics were determined: age at index date, gender, HbA_{1c} at index

date, the proportion of prior complications at index date, newly treated, follow-up, number of HbA_{1c} measurements during follow-up, and BMI at index date. Newly treated patients were defined as patients without any AHA prescription in the year prior to index date.

Outcomes

Diabetic foot, retinopathy, and renal complications were the microvascular events of interest, and coronary artery disease (CAD) and cerebrovascular disease were the macrovascular events of interest. All complications were based on GP-recorded information.

Microvascular complications

Diabetic foot was identified based on recorded codings and text searches for the diagnoses of necrosis, ulcer, diabetic foot, infection, wound, erysipelas, gangrene, Charcot foot, loss of protective sensation, peripheral artery disease, peripheral arterial occlusive disease, claudication, neuropathy, and amyotrophy.[15,16] The positive clinical assessments of necrosis and ulcers were also included.

Retinopathy was identified based on ICPC code F83 (retinopathy), positive outcomes of retinopathy assessments, and text searches for the diagnoses of retinopathy, maculopathy, or diabetic macular oedema.

Renal complications were identified based on multiple assessments of the estimated glomerular filtration rate <60 ml/min/1.73 m^2 [modification of the Diet in Renal Disease (MDRD) formula] or proteinuria (albumin >30 mg/l), at least 90 days and at most 365 days apart, or on searches for the diagnoses of nephropathy, nephrotic syndrome, glomerular haematuria, glomerulonephritis, nephrosis, kidney failure, dialysis, transplants, proteinuria and albuminuria.

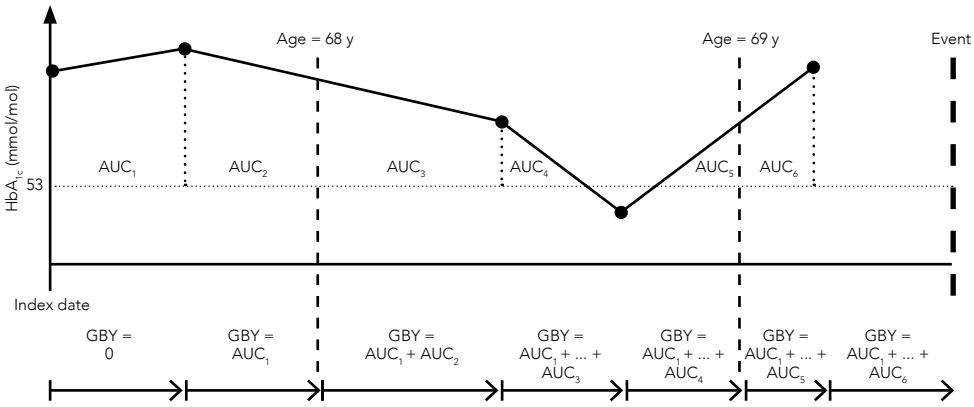
Macrovascular complications

The identification of CAD was based on ICPC codes K53 (coronary artery angioplasty), K74 (angina pectoris), K75 (myocardial infarction), and K76 (ischemic heart disease), and searches for the diagnoses of angina pectoris, acute coronary syndrome (ACS), and myocardial infarction. Cerebrovascular disease–related events were identified based on ICPC codes K89 [transient ischemic attack (TIA)] and K90 [stroke/cerebrovascular accident (CVA)], as well as searches for the diagnoses of stroke, cerebral infarction, CVA and TIA.

Glycaemic exposure

Four different definitions of glycaemic exposure were studied. A first definition of exposure was based on the HbA_{1c} at index,[3,17,18] defined as the last HbA_{1c} measurement in the year prior to the index date. A second definition of glycaemic exposure was based on all observed HbA_{1c} measures during post-index follow-up; HbA_{1c} was included as a time-dependent covariate. The third approach was similar to the previous one, but instead of including observed HbA_{1c}-values the exponential moving average (EMA) of HbA_{1c} was included as a time-dependent covariate. The EMA is a variant of the updated mean.[1,17] In this measure, the current HbA_{1c}

measurement amounts to 20% of the calculated value and the previously calculated EMA amounts to 80%. The EMA was chosen to ensure that, independent of the total number of measurements, the last measurement is given a fixed weight of 0.2. In a fourth approach, the glycaemic burden was calculated, defined as the AUC given a threshold of 53 mmol/mol (7%).[13] Between two HbA_{1c} measurements a linear interpolation was used and the glycaemic burden over a time period was calculated when either a new HbA_{1c} measurement occurred or the age of a patient changed. At the start of a given time period, the cumulative glycaemic burden was defined as the sum of all the calculated AUCs up until then. Furthermore, the cumulative glycaemic burden is divided by 365 to express the value in years. The calculation of the glycaemic burden years (GBY) is presented graphically in Fig. 1. The GBY was included as a time-dependent variable in the Cox-model.



Abbreviations: AUC, area under the curve; GBY, glycaemic burden year

Fig. 1 Calculation of GBYs

Partial GBYs (AUC_1, AUC_2, etc.) were calculated per interval between cut-off points as the difference in HbA_{1c} above the threshold of 53 mmol/mol (7%) multiplied by the number of years between those points. Cut-off points were HbA_{1c} measurements, changes in age, or interpolation lines crossing the threshold. Cumulative GBY was updated at each of the cut-off points by summing all prior GBYs.

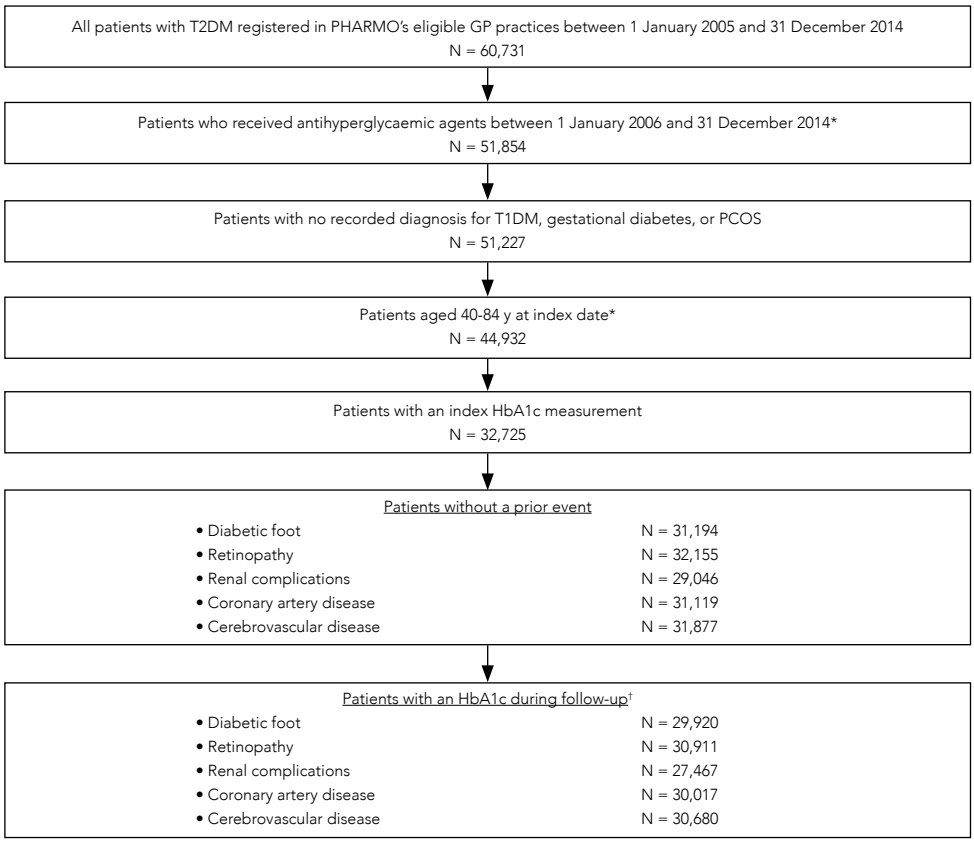
Statistical analysis

Population characteristics were reported as absolute and relative frequencies (n, %) for categorical variables and as median and interquartile range (IQR) for continuous variables, if applicable. Incidence rates (IRs) were calculated per type of event by dividing the number of patients with an event by the total number of patient-years at risk (summed durations of total

treatment period, censored at the time of the event under investigation).
A Cox proportional hazards regression analysis was performed for each of the micro- and macrovascular complications with each of the four glycaemic exposure measures. The PROC PHREG procedure from SAS 9.4 was used.
For the model, using HbA_{1c} at index, the Cox proportional hazards regression model was adjusted for age, gender, and the year of index. For illustration, the HbA_{1c} value at index was categorized as <53 mmol/mol (7%), 53 to <64 mmol/mol (7 to <8%) and ≥64 mmol/mol (8%). For the other models, repeated measurements of HbA_{1c} were included and a time-dependent Cox proportional hazards regression analysis was performed. Age and the measure of exposure (HbA_{1c}, EMA or GBY) were used as time-dependent variables, and the model was corrected for age, gender, the year of index, and time (in years) since the first measurement above 53 mmol/mol (7%) and the time (in years) since the last measurement below 53 mmol/mol (7%). The time-dependent HbA_{1c} and the EMA were categorized as follows: <53 mmol/mol (7%), 53 to <64 mmol/mol (7 to <8%) and ≥64 mmol/mol (8%). The categorization of glycaemic burden was based on its distribution: 0 (reference), >0 to ≤1, >1 to ≤3 and >3 GBYs.

Results

Patients
The flow chart describing the process of patient selection is shown in Fig. 2. After applying all inclusion and exclusion criteria, approximately 30,000 patients were included per outcome. The characteristics of the total population, without exclusions of patients with prior events, are shown in Table 1. Median (IQR) age was 65 (57-73) years, and approximately half of the patients were female (47%). At index date, 50% of the patients were on target [HbA_{1c} <53 mmol/mol (7%)], and only 18% of the patients had an HbA_{1c} at index ≥64 mmol/mol (8%). The incidence rates of the micro- and macrovascular events are presented in Table 2. The incidence rate of microvascular events ranges from 2.5 new retinopathy cases per 100 patient-years (PYs) to 6.0 new renal complication cases per 100 PYs, and the incidence rates of macrovascular events were between 1 and 1.4 events per 100 PYs.



*The first antihyperglycaemic prescription after at least 1 year of enrolment in the database; †Follow-up differed per event of interest as patients were followed from index date to end of follow-up (i.e., first occurrence of event of interest, death, loss to follow-up in the PHARMO Database Network, or end of study period [31 December 2014], whichever occurred first). Abbreviations: GP, general practitioner; PCOS, polycystic ovary syndrome; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Fig. 2 Flow chart of patient selection

INDEX

Glycaemic exposure

In total, 20 analyses were performed, and the results are presented in Fig. 3 and summarized in Supplemental Table S1. The results of the different events are plotted separately, with the hazard ratios (HRs) on the vertical axis. Within each plot, the four different measures of glycaemic exposure are displayed with the HR per categorized variable.

Table 1 Characteristics of patients with T2DM

	Total N = 32,725
Age at index date, years	
Median (IQR)	65 (57-73)
Gender, n (%)	
Male	17,270 (53)
Female	15,455 (47)
HbA_{1c} at index date, n (%)	
<53 mmol/mol (7%)	16,325 (50)
53 mmol/mol (7%) to <58 mmol/mol (7.5%)	6,582 (20)
58 mmol/mol (7.5%) to <64 mmol/mol (8%)	3,771 (12)
≥64 mmol/mol (8%)	6,047 (18)
Median (IQR)	53.0 46.4-59.6)
Prior complications at index date, n (%)	
Microvascular	
Diabetic foot	1,531 (5)
Retinopathy	570 (2)
Renal complications	3,679 (11)
Macrovascular	
Coronary artery disease	1,526 (5)
Cerebrovascular disease	848 (3)
Newly treated	
Yes 13,656 (42)	
No 19,069 (58)	
Follow-up, years	
Median (IQR)	5.4 (2.5-7.8)
Number of HbA1c measurements	
Median (IQR)	18.0 (8.0-29.0)
BMI, kg/m^2	
Median (IQR)	29.7 (26.8-33.3)

BMI body mass index, IQR interquartile range, T2DM type 2 diabetes mellitus. *BMI was determined in the year prior to index date and was available for 65% of the patients.

Table 2 Incidence rates (95% CI) of micro- and macrovascular complications

	$N_{at\ risk}$	$PY_{at\ risk}$	N_{events}	IR/100 PY (95% CI)
Microvascular complications				
Diabetic foot	31,194	147,440	3,904	2.65 (2.57-2.73)
Retinopathy	32,155	150,465	3,764	2.50 (2.42-2.58)
Renal complications	29,046	124,708	7,507	6.02 (5.88-6.16)
Macrovascular complications				
Coronary artery disease	31,199	151,921	2,129	1.40 (1.34-1.46)
Cerebrovascular disease	31,877	156,966	1,664	1.06 (1.01-1.11)

CI confidence interval, IR incidence rate, PY patient-year

The results for the first model, using only the HbA_{1c} at index, suggested an increased risk for higher HbA_{1c} values for the microvascular complications as well as CAD. However, the results were only significant for the highest category [HbA_{1c} ≥64 mmol/mol (8%)] for renal complications [HR (95% CI) of 1.10 (1.02-1.18)] and CAD [HR (95% CI) of 1.18 (1.04-1.34)] compared to the reference category [HbA_{1c} <53 mmol/mol (7%)].

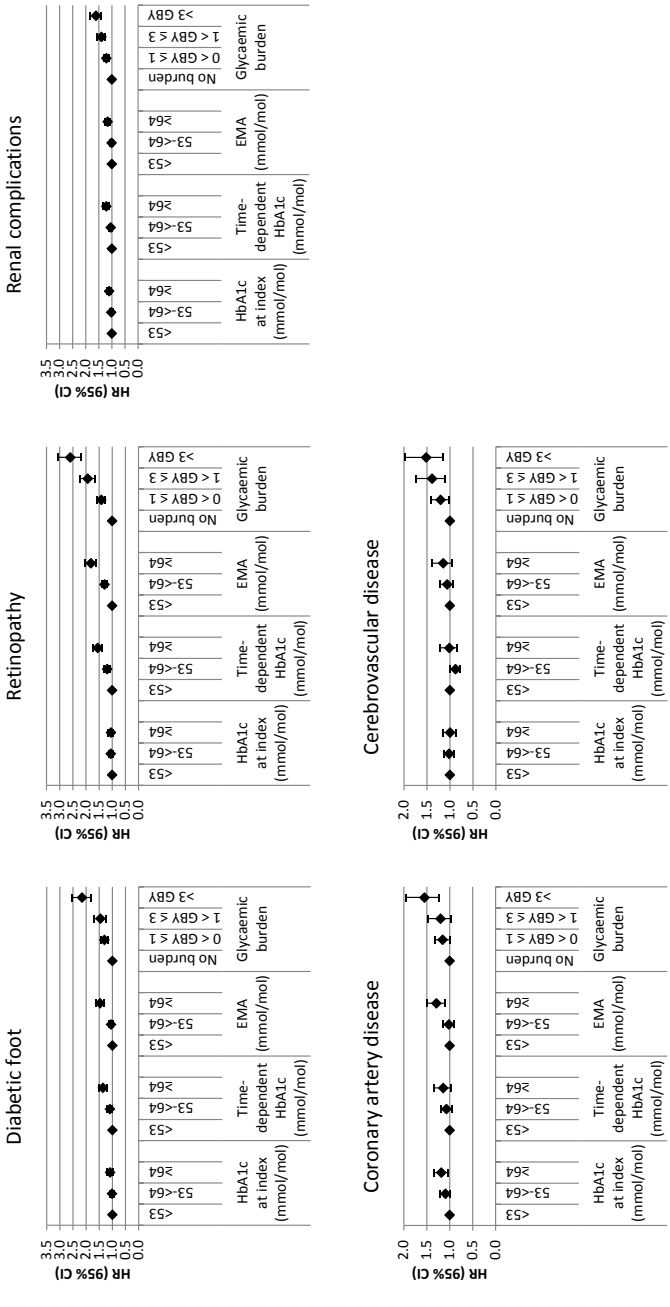
The results for the time-dependent HbA_{1c} model showed an increased risk for both diabetic foot and retinopathy. For diabetic foot, the HRs (95% CI) for the middle and highest HbA_{1c} categories were 1.09 (1.00-1.19) and 1.36 (1.21-1.52), respectively. For retinopathy, this was 1.19 (1.10-1.30) and 1.55 (1.40-1.73), respectively. For renal complications, only the highest HbA_{1c} category showed a significant association [HR (95% CI): 1.20 (1.10-1.31)]. The associations between time-dependent HbA_{1c} and macrovascular complications were not significant.

The results for the third model, using the EMA, were very similar to the results of the previous model with a few notable exceptions. Specifically, the HRs for retinopathy were markedly higher for both the middle and highest HbA_{1c} categories (i.e., HRs (95% CI) of 1.29 (1.18-1.41) and 1.81 (1.63-2.02), respectively]. Also, the results for CAD were significant for the highest category [HbA_{1c} ≥64 mmol/mol (8%); HR (95% CI) of 1.29 (1.10-1.50)].

The results for the glycaemic burden model showed significantly increased risks associated with higher GBY levels for the microvascular complications. For diabetic foot, the HRs were 1.30, 1.46 and 2.15 for >0 to ≤1, >1 to ≤3 and >3 GBYs, respectively, compared to the reference category of no glycaemic burden. For retinopathy, the HRs ranged from 1.41 to 2.60, and for renal complications, the HRs ranged from 1.20 to 1.61. The macrovascular complications showed similar results. However, for CAD GBY >1 to ≤3, the HR was not significantly higher. Cerebrovascular disease on the other hand did show a dose response relation where the HRs ranged from 1.20 to 1.52.

Additional results of the models, including the covariates, are included in Online Resource 1 (Supplemental Table S2).

INDEX



CI confidence interval, EMA exponential moving average, HR hazard ratio

Fig. 3 Association between different measures for glycaemic exposure and micro- and macrovascular complications

Discussion

Main findings

All micro- and macrovascular complications were weakly associated with exposure to high HbA_{1c} [HbA_{1c} ≥64 mmol/mol (8%)] at index to some extent, but this was only significant for renal complications [HR (95% CI) of 1.10 (1.02-1.18)] and CAD [HR (95% CI) of 1.18 (1.04-1.34)]. When modelling glycaemic exposure as the time dependent observed HbA_{1c}, a significantly increased risk for all microvascular complications was observed for HbA_{1c} ≥64 mmol/mol (8%). For the macrovascular events, this model was inconclusive, and the results were not significant. These results are largely in line with other findings. For renal complications, Gerstein et al.[17] found an association between an increase in HbA_{1c} at index and nephropathy, and Klein[3] found an association between an increase in HbA_{1c} at index and both gross proteinuria and renal failure. For diabetic foot, an increased risk was expected for the model using the HbA_{1c} value at index in concordance with earlier findings[3,18]; however, these studies found associations with either amputation[3] or sensory neuropathy[18], while we defined a composite endpoint covering a broad spectrum of peripheral arterial problems. However, our findings do suggest that the most recent HbA_{1c} measurement (i.e., time-dependent HbA_{1c}) is a better predictor for diabetic foot than the HbA_{1c} at index. For CAD, the results regarding HbA_{1c} at index are in concordance with literature[10] where a HR (95% CI) of 1.05 (1.00-1.10) was reported for a 1% increase in HbA_{1c} also using the HbA_{1c} at index. On the other hand, no significant effect was found for the time-dependent HbA_{1c}, suggesting that the HbA_{1c} at index is a better predictor for CAD than the most recent HbA1c measurement. The results for cerebrovascular disease were inconclusive, which is in line with other findings[10] where an HR (95% CI) of 0.96 (0.88-1.06) for a 1% increase of HbA_{1c} at index was reported. The EMA-based results for the microvascular events showed similar results as the time-dependent HbA_{1c}. Retinopathy specifically showed a clear dose response for EMA, and associations were stronger than in the time-dependent HbA_{1c} model. For the macrovascular event of CAD, a significantly increased risk was observed in the highest risk category [EMA ≥ 64 mmol/mol (8%)]. Again, the results for cerebrovascular disease were inconclusive. An association between the increase in updated mean HbA_{1c} and the risk has been reported for diabetic foot,[1] retinopathy,[8,19] renal failure,[17] CAD[1,2] and cerebrovascular disease[1]. With the exception of cerebrovascular disease, our results reflected previously reported findings. Absence of an association between EMA and the risk of cerebrovascular disease may be explained by the fact that we defined cerebrovascular disease as a composite endpoint including stroke, TIA, CVA, and cerebral infarction, while Stratton et al.[1] reported a HR (95% CI) of 1.14 (1.01-1.27) for a 1% increase in updated mean HbA_{1c} for stroke only. For the microvascular events, the analyses using glycaemic burden showed the clearest dose response. Overall, the HRs were higher, but the categories used were different from the previous models and not directly comparable as the GBY categories of this cumulative outcome were based on the distribution of the number of patients rather than clinically recognizable cut-off points for HbA_{1c}. Again, the effects for retinopathy were stronger than

INDEX

for the other microvascular events: the HRs ranged from 1.41 to 2.60 against 1.30-2.15 for diabetic foot and 1.20-1.61 for renal failure. Maple-Brown et al.[13] used the AUC as a measure for chronic glycaemic exposure and found that it was a good predictor for microvascular complications. For the macrovascular events, CAD (GBY >0 to ≤1 and GBY >3) showed a significant association. Cerebrovascular disease showed a significant, albeit small, dose response with HRs ranging from 1.20 to 1.51.

Strengths and limitations

A strength of the study is the use of a large population in a real-world setting with long follow-up. Data from GPs in The Netherlands is especially suited, since diabetes care in The Netherlands is highly organized, and the majority (90%-95%) of T2DM patients are treated within the primary care setting. This means that we were able to validate our models in actual clinical practice.

A limitation is that the duration of diabetes was not included in the model because it is not always explicitly recorded as a clinical parameter. We also did not differentiate between patients who were and were not newly treated. Both have resulted in underestimation of the glycaemic burden and are likely to have resulted in an underestimation of the associations. However, available data reflects the situation in the daily practice of any physician, who will not always know the glycaemic history of a patient and will act on the data available at the time of a visit. Furthermore, we performed post hoc analyses, correcting for newly initiated or prevalent use of AHA at the time of the index date, to test whether underestimation of the glycaemic burden of patients that were already treated at the start of their recorded history might have caused underestimation of the associations with complications. The results were very similar to the main analysis and therefore could not support this assumption. This means that even with incomplete records, all available history of a patient may provide valuable information to a physician regarding the build-up of glycaemic memory. One of the limitations of real-world evidence in general is that information is not collected or recorded for the purpose of doing research. Changes in disease management have had a major impact on the way complications were recorded during the study period, leading to more detailed outcome recording over time. To allow analysis of more or less similar outcomes over time, composite endpoints had to be used. For example, in the case of diabetic foot, this resulted in a mix of micro- and macrovascular causes. This loss of specificity may have weakened this association of specific contributing factors within the composite. Future studies may be able to clarify specific associations by using more specific outcome definitions. In 2006, an integrated diabetes care program was introduced, with structured management and regular check-ups of the patient by an interdisciplinary team of GPs, diabetes nurses, podiatrists and ophthalmologists. Check-ups include assessment of HbA_{1c}, renal function, retinopathy, (early) signs of diabetic foot and history taking with regard to macrovascular complications. The gradual rollout of this integrated care was boosted by financial incentives linked to developing performance indicators offered by healthcare insurance companies to GPs from mid-2007 onward. This is reflected in the data by a steady

increase in the recorded number of complications, which was about fivefold over the whole study period. As 40% of our population had an index date before 2008, this means that a significant number of patients may have been misclassified as having no complications at index date, and that some complications now registered as newly developed may have been pre-existing. Incidence rates may therefore have been overestimated. As this possible misclassification was most likely irrespective of HbA_{1c} levels, we do not believe that this non-differential misclassification has influenced our results to a large extent. Finally, we have not taken treatment into account, while the type of treatment may influence outcomes through other mechanisms than glucose lowering. For future research, it would be very valuable to take the type of treatment and other potential risk factors into account.

Implications for clinical practice

The first two models used a single point measurement as a predictor for outcomes, where this single point can either be static (i.e., HbA_{1c} at index) or time updating (i.e., time-dependent HbA_{1c}). The static model is highly practical for database studies, while the time-updating model better reflects the interpretation a physician might apply in daily practice (i.e., use of the last known value for risk assessment). However, it should be noted that the results of the current study show that neither of these models is necessarily a good representation of the risk to which an individual is exposed. The EMA, on the other hand, shows a stronger relation with diabetic foot, retinopathy and CAD, if not with the other outcomes, which does suggest that glycaemic memory plays a role in these outcomes. This is further corroborated by the results of the glycaemic burden model where these associations are more pronounced and even become apparent for the macrovascular complications. Given that the glycaemic burden model gives a better discrimination between patients that do or do not develop complications, it is a very promising method for further research into the long term effects of hyperglycaemia. This could contribute valuable evidence to influence clinical decision making. All in all, the results from this study show that longer exposure to HbA_{1c} levels above target is associated with increased risk of both micro- and macrovascular complications. Furthermore, the results suggest that glycaemic memory plays a role in the development of diabetes complications and that treatment inertia increases the risk of these outcomes in broad populations of patients with T2DM who are not on target.[20] From the individual patient perspective, however, it is important to note that intensive glucose-lowering treatment aiming at a low target HbA_{1c} may lead to increased risk of hypoglycaemia or adverse drug reactions and therefore is not recommended for patients of older age or with short life expectancy, important comorbidities, or poor self-care capabilities.[6] That is why the most recent revision of the diabetes guidelines for T2DM[21] has included higher targets for patients over 70 years of age who cannot be managed with metformin alone. Our finding that glycaemic memory plays an important role in development of complications emphasizes the importance of physicians keeping in mind that lower targets are probably more beneficial for a patient, provided that they are attainable without the trade-off of increased immediate risk. This underlines the need for frequent and active monitoring of the diabetes patient.

Conclusion

This study shows that greater and more prolonged exposure to hyperglycaemia is associated with increased risk of both micro- and macrovascular complications. The possibility of damage caused by clinical inertia is something that needs to be addressed in clinical practice.

Acknowledgements

The authors would like to thank all the healthcare providers contributing information to the database included in this study. This work was supported by the Dutch Diabetes Research Foundation (grant no 2014.00.1753) and sponsored by Janssen Pharmaceutica NV. Sponsorship for this study and article processing charges were funded by Janssen Pharmaceutica NV. Technical editorial assistance was provided by Shannon O'Sullivan, ELS, of MedErgy and funded by Janssen Pharmaceutica NV. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval to the version to be published. Rients P. T. van Wijngaarden, Jetty A. Overbeek, Edith M. Heintjes, Agata Schubert, Joris Diels, Huub Straatman, Ewout W. Steyerberg and Ron M. C. Herings contributed to the conception and the design of the study. Rients P. T. van Wijngaarden, Jetty A. Overbeek and Huub Straatman performed the analyses. Rients P. T. van Wijngaarden (the manuscript's guarantor) affirms that the manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Disclosures

The PHARMO Institute for Drug Outcomes Research reports grants from Janssen-Cilag. Rients P. T. van Wijngaarden is an employee of the PHARMO Institute. Jetty A. Overbeek is an employee of the PHARMO Institute. Edith M. Heintjes is an employee of the PHARMO Institute. Huub Straatman is an employee of the PHARMO Institute. Ron M.C. Herings is an employee of the PHARMO Institute. The PHARMO Institute is an independent research institute and performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. Agata Schubert is a full-time employee of Janssen-Cilag Poland. Joris Diels is a full-time employee of Janssen Research & Development. Ewout W. Steyerberg has nothing to disclose.

Compliance with Ethics Guidelines

This article does not contain any new studies with human or animal subjects performed by any of the authors.

INDEX

Data Availability

Requests for sharing study data must be made on specific grounds either with the aim to corroborate the study results in the interest of Public Health or in the context of an audit by a competent authority. Sufficient information needs to be provided to confirm that the request is made for one of the above-mentioned purposes, including a wound justification and, in case of a request with a view to corroborate study results, a protocol on the research for which the data will be used or a plan for quality control checks, as applicable.

INDEX

References

1. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. **BMJ**. 2000;7258:405-412.
2. Zhang Y, Hu G, Yuan Z, et al. Glycosylated hemoglobin in relationship to cardiovascular outcomes and death in patients with type 2 diabetes: a systematic review and meta-analysis. **PLoS One**. 2012;8:e42551.
3. Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. **Diabetes Care**. 1995;2:258-268.
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). **Lancet**. 1998;9131:837-853.
5. Jeffcoate SL. Diabetes control and complications: the role of glycated haemoglobin, 25 years on. **Diabet Med**. 2004;7:657-665.
6. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. **Diabetes Care**. 2015;1:140-149.
7. Khunti K, Wolden ML, Thorsted BL, et al. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. **Diabetes Care**. 2013;11:3411-3417.
8. Yoshida Y, Hagura R, Hara Y, et al. Risk factors for the development of diabetic retinopathy in Japanese type 2 diabetic patients. **Diabetes Res Clin Pract**. 2001;3:195-203.
9. Araki S, Haneda M, Sugimoto T, et al. Factors associated with frequent remission of microalbuminuria in patients with type 2 diabetes. **Diabetes**. 2005;10:2983-2987.
10. Lind M, Odén A, Fahlén M, et al. A Systematic Review of HbA1c Variables Used in the Study of Diabetic Complications. **Diabetes & Metabolic Syndrome: Clinical Research & Reviews**. 2008;282-293.
11. Bailey CJ, Day C. Glycemic memory. **The British Journal of Diabetes & Vascular Disease**. 2008;5:242-247.
12. Lind M, Odén A, Fahlén M, et al. The true value of HbA1c as a predictor of diabetic complications: simulations of HbA1c variables. **PLoS One**. 2009;2:e4412.
13. Maple-Brown L, Ye C, Retnakaran R. Area-under-the-HbA1c-curve above the normal range and the prediction of microvascular outcomes: an analysis of data from the Diabetes Control and Complications Trial. **Diabetic Medicine**. 2013;1:95-99.
14. Rutten GEHM, De Grauw WJC, Nijpels G, et al. NHG-Standaard Diabetes mellitus type 2 (Tweede herziening). **Huisarts Wet**. 2006;3:137-152.
15. Jain AKC, Joshi S. Diabetic foot classifications: Review of literature. **Medicine science**. 2013;3:715-721.

16. Fincke BG, Miller DR, Turpin R. A classification of diabetic foot infections using ICD-9-CM codes: application to a large computerized medical database. **BMC Health Services Research**. 2010;1:192.
17. Gerstein HC, Pogue J, Mann JF, et al. The relationship between dysglycaemia and cardiovascular and renal risk in diabetic and non-diabetic participants in the HOPE study: a prospective epidemiological analysis. **Diabetologia**. 2005;9:1749-1755.
18. Adler AI, Boyko EJ, Ahroni JH, et al. Risk factors for diabetic peripheral sensory neuropathy. Results of the Seattle Prospective Diabetic Foot Study. **Diabetes Care**. 1997;7:1162-1167.
19. Araki A, Ito H, Hattori A, et al. Risk factors for development of retinopathy in elderly Japanese patients with diabetes mellitus. **Diabetes Care**. 1993;8:1184-1186.
20. Cardoso CR, Leite NC, Ferreira MT, et al. Prognostic importance of baseline and serial glycated hemoglobin levels in high-risk patients with type 2 diabetes: the Rio de Janeiro Type 2 Diabetes Cohort Study. **Acta Diabetol**. 2015;1:21-29.
21. Rutten GEHM DGW, Nijpels G, Houweling ST, Van de Laar FA, Bilo HJ, Holleman F, Burgers JS, Wiersma Tj, Janssen PGH. NHG-Standaard Diabetes mellitus type 2 (derde herziening). **Huisarts Wet** 2013; 512-525.

Supplementary Material

Supplemental Table S1 Association between different measures of glycaemic exposure and micro- and macrovascular complications adjusted for covariates

	Diabetic foot HR (95% CI)	Retinopathy HR (95% CI)	Renal complications HR (95% CI)	CAD HR (95% CI)	Cerebrovascular disease HR (95% CI)
HbA_{1c} at index					
<53 mmol/mol	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
53-<64 mmol/mol	1.01 (0.94- 1.09)	1.05 (0.98-1.13)	1.02 (0.97-1.08)	1.09 (0.99-1.20)	1.02 (0.91-1.14)
≥64 mmol/mol	1.08 (0.99-1.19)	1.05 (0.96-1.15)	1.10 (1.02-1.18)	1.18 (1.04-1.34)	1.00 (0.86-1.16)
Time-dependent HbA_{1c}					
<53 mmol/mol	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
53-<64 mmol/mol	1.09 (1.00-1.19)	1.19 (1.10-1.30)	1.04 (0.98-1.11)	1.07 (0.96-1.20)	0.88 (0.77-1.00)
≥64 mmol/mol	1.36 (1.21-1.52)	1.55 (1.40-1.73)	1.20 (1.10-1.31)	1.14 (0.97-1.33)	1.02 (0.85-1.22)
EMA					
<53 mmol/mol	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
53-<64 mmol/mol	1.05 (0.96-1.14)	1.29 (1.18-1.41)	1.00 (0.94-1.07)	1.02 (0.91-1.14)	1.06 (0.93-1.21)
≥64 mmol/mol	1.47 (1.32-1.64)	1.81 (1.63-2.02)	1.15 (1.06-1.26)	1.29 (1.10-1.50)	1.15 (0.95-1.38)
GBYs					
0 (no burden)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>0-1	1.30 (1.17-1.45)	1.41 (1.26-1.58)	1.20 (1.12-1.30)	1.15 (1.00-1.33)	1.20 (1.02-1.41)
>1-3	1.46 (1.25-1.69)	1.93 (1.67-2.24)	1.39 (1.25-1.55)	1.20 (0.98-1.46)	1.39 (1.11-1.73)
>3	2.15 (1.82-2.54)	2.60 (2.19-3.07)	1.61 (1.41-1.83)	1.55 (1.23-1.95)	1.52 (1.16-1.98)

Abbreviations: CAD, coronary artery disease; CI, confidence interval; EMA, exponential moving average; GBY, glycaemic burden year; HR, hazard ratio

INDEX

Supplemental Table S2 Association between covariates and micro- and macrovascular complications adjusted for different measures for glycaemic exposure

	HbA_{1c} at index HR (95% CI)	Time-dependent HbA_{1c} HR (95% CI)	EMA HR (95% CI)	GBYs HR (95% CI)
Diabetic foot, adjusted for				
Age, y	1.00 (1.00-1.01)	1.03 (1.03-1.04)	1.03 (1.03-1.04)	1.03 (1.03-1.04)
Gender, female	1.05 (0.99-1.13)	1.02 (0.96-1.09)	1.02 (0.96-1.09)	1.02 (0.96-1.09)
Time since first time above threshold, y	-	1.03 (1.00-1.05)	1.02 (0.99-1.05)	0.98 (0.95-1.01)
Time since last time above threshold, y	-	0.99 (0.97-1.02)	0.99 (0.96-1.02)	1.02 (0.99-1.05)
Year of index	1.49 (1.46-1.53)	1.04 (1.02-1.06)	1.03 (1.01-1.05)	1.03 (1.02-1.05)
Retinopathy, adjusted for				
Age, y	1.01 (1.00-1.01)	1.01 (1.01-1.02)	1.01 (1.01-1.02)	1.01 (1.01-1.02)
Gender, female	1.05 (0.99-1.12)	1.04 (0.97-1.11)	1.04 (0.97-1.11)	1.04 (0.97-1.11)
Time since first time above threshold, y	-	1.13 (1.10-1.16)	1.11 (1.08-1.15)	1.05 (1.02-1.09)
Time since last time above threshold, y	-	0.99 (0.96-1.02)	1.00 (0.97-1.03)	1.02 (0.99-1.06)
Year of index	1.57 (1.54-1.61)	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.98 (0.96-1.00)
Renal complications, adjusted for				
Age, y	1.01 (1.01-1.01)	1.05 (1.05-1.06)	1.05 (1.05-1.06)	1.05 (1.05-1.06)
Gender, female	1.09 (1.04-1.15)	1.04 (0.99-1.09)	1.04 (0.99-1.09)	1.04 (0.99-1.09)
Time since first time above threshold, y	-	1.09 (1.07-1.12)	1.09 (1.07-1.12)	1.05 (1.03-1.08)
Time since last time above threshold, y	-	1.06 (1.04-1.09)	1.05 (1.03-1.08)	1.09 (1.06-1.11)
Year of index	1.50 (1.47-1.52)	0.98 (0.97-1.00)	0.98 (0.97-1.00)	0.98 (0.97-1.00)
CAD, adjusted for				
Age, y	1.04 (1.03-1.04)	1.04 (1.03-1.04)	1.04 (1.03-1.04)	1.04 (1.03-1.04)
Gender, female	1.47 (1.35-1.61)	1.48 (1.35-1.62)	1.48 (1.35-1.62)	1.48 (1.35-1.61)
Time since first time above threshold, y	-	1.04 (1.00-1.08)	1.03 (0.99-1.07)	1.01 (0.97-1.05)
Time since last time above threshold, y	-	1.00 (0.96-1.05)	1.00 (0.96-1.04)	1.02 (0.98-1.06)
Year of index	0.94 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)	0.95 (0.92-0.97)
Cerebrovascular disease, adjusted for				
Age, y	1.01 (1.00-1.01)	1.07 (1.06-1.07)	1.07 (1.06-1.07)	1.07 (1.06-1.07)
Gender, female	1.08 (0.98-1.20)	1.15 (1.04-1.27)	1.15 (1.04-1.27)	1.15 (1.04-1.27)
Time since first time above threshold, y	-	1.04 (0.99-1.08)	1.03 (0.99-1.08)	1.00 (0.96-1.05)
Time since last time above threshold, y	-	0.99 (0.95-1.04)	1.02 (0.97-1.06)	1.04 (1.00-1.09)
Year of index	1.47 (1.42-1.52)	1.01 (0.98-1.04)	1.00 (0.98-1.03)	1.00 (0.98-1.03)

Abbreviations: CAD, coronary artery disease; CI, confidence interval; EMA, exponential moving average; GBY, glycaemic burden year; HR, hazard ratio; y, years

INDEX

INDEX

CHAPTER 6

Risk of dipeptidyl peptidase-4 (DPP-4) inhibitors on site-specific cancer: A systematic review and meta-analysis

Jetty A. Overbeek, Marina Bakker, Amber A.W.A. van der Heijden, Myrthe P.P. van Herk-Sukel, Ron M.C. Herings, Giel Nijpels

Diabetes Metab Res Rev. 2018 Jul;34(5):e3004. doi: 10.1002/dmrr.3004. Epub 2018 Apr 26

Abstract

Background: The long-term impact of dipeptidyl peptidase-4 (DPP-4) inhibition is unknown and there are concerns about the influence of DPP-4 inhibition on carcinogenesis of the pancreas and thyroid. As DPP-4 is a rather unselective enzyme present in many tissues, we focused on all specific cancer types.

Methods: PubMed and EMBASE were searched between January 2005 and April 2017 to identify studies comparing DPP-4 inhibitors with either placebo or active drugs on cancer risk. Studies were included if they reported on at least one specific cancer outcome and had a follow-up of at least 1 year after start of drug use. Methodological quality of the studies was assessed by the Cochrane Collaboration's tool and the Newcastle-Ottawa Scale.

Results: Twenty-five studies met the inclusion criteria (12 randomized controlled trials and 13 observational studies). Sample sizes of the DPP-4 inhibitor groups ranged from 29 to 8212 patients for randomized controlled trials and from 2422 to 71 137 patients for observational studies. Mean age ranged from 51 to 76 years, and mean follow-up was 1.5 years. None of the pooled (sensitivity) analyses, except the observational studies studying breast cancer (hazard ratio [95%CI]: 0.76 [0.60-0.96]), showed evidence for an association between DPP-4 inhibitors and site-specific cancer. Also for pancreatic and thyroid cancer, no statistically significant risk was found.

Conclusion: Based on the current literature, it is not possible to conclude whether DPP-4 inhibitors were associated with an increased risk of site-specific cancer. Future studies should address the methodological limitations and follow patients for a longer period in order to determine the long-term cancer risk of DPP-4 inhibitors.

INDEX

Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors, or gliptins, are a class of oral hypoglycaemic drugs that are used to reach glycaemic control in people with type 2 diabetes mellitus (T2DM). Currently, 5 DPP-4 inhibitors are approved in Europe: sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin.

Dipeptidyl peptidase-4 is a rather unselective enzyme involved in many physiological processes. The substrates of DPP-4 include growth factors, chemokines, neuropeptides, and vasoactive peptides. Furthermore, DPP-4 plays a major role in glucose metabolism and is responsible for the degradation of incretins such as glucagon-like-peptide-1 (GLP-1). Glucagon-like-peptide-1 receptors are also present in many tissues, including thyroid, exocrine pancreas, meninges, renal tubules, and bone, and their activation results in changes entirely unrelated to glucose homeostasis.[1]

Studies using the Food and Drug Administration (FDA) Adverse Event Reporting System suggested an increased risk of acute pancreatitis and pancreatic cancer associated with the use of incretin-based drugs, i.e., DPP-4 inhibitors and GLP-1 receptor agonists.[2,3] In that context, the FDA and the European Medicines Agency undertook independent reviews of all clinical and preclinical data related to the possible association of incretin-based drugs with pancreatic safety and especially pancreatic cancer. In 2014, a joint study was published in the New England Journal of Medicine, stating that the agencies had not yet reached a final conclusion regarding a possible relationship.[4] Since then, several literature reviews have been conducted regarding incretin-based drugs and pancreatic cancer.[5-9]

However, as DPP-4 inhibitors are involved in many physiological processes, the influence of DPP-4 inhibitors might be more far reaching than the influence on the glucose homeostasis. There is evidence in animal models that DPP-4 inhibition is related to pancreatic cancer, ovarian cancer, neuroblastoma, prostate cancer, melanoma, and lung cancer.[10] Immunomodulatory effects of DPP-4 inhibition might explain the increased risk for all cancers. Furthermore, the biologic features of cancer vary in relation to their tissue of origin, and global measures of cancer risk may therefore mask the potential impact of a specific therapeutic agent upon a specific type of cancer.[11]

Therefore, the objective of this systematic review was to conduct a meta-analysis to summarize evidence on the association between DPP-4 inhibitors and the incidence of all specific cancer types.

Materials and methods

Search strategy

The PubMed and EMBASE databases were searched for literature published between January 1, 2005 (date of first DPP-4 inhibitor publication), and April 4, 2017 (date of search). A search string combining terms on cancer and DPP-4 inhibitors was built (Data S1).

Inclusion and exclusion criteria

Only primary studies, such as trials and observational studies, relevant for the research objective were included. The reference lists of systematic reviews were checked to identify additional relevant primary studies. Publications that compared DPP-4 inhibitors with either placebo or active antidiabetic drugs were included. As overall cancer incidence is likely to mask variations in specific patterns of site-specific cancer incidence,[12] publications focusing on overall cancer incidence only were excluded. Studies with follow-up of less than 52 weeks were excluded, to keep detection bias or even reverse causality to a minimum. These biases can be the result of a diagnostic (protopathic) bias, i.e., an increased odd of detecting cancer shortly after the initiation of a new glucose lowering drug.[13]

Based on growth rates of human malignant tumours,[14] it is not likely that cancers diagnosed in the year after initiation of the new glucose lowering are causally related to initiation of the drug. Other exclusion criteria were studies on biochemistry or molecular studies and animal studies. The complete list of exclusion criteria can be found in Figure 1. When studies did not report sufficient information regarding risk or variables needed to calculate the risk, authors were contacted. Only if the required information was obtained, the study was included.

INDEX

Selection process

Relevant publications were selected by a 3-step selection procedure. First, titles and abstracts identified through the search strategy were assessed on relevancy for the objectives. All titles and abstracts were screened in duplicate by 2 independent researchers. Disagreements were resolved by a third researcher. Second, the full text publications, selected in the first step, were screened by the same 2 researchers and independently checked by a third reviewer. It was determined whether the paper indeed answered the study objective. Finally, further scrutiny of publications during the data-extraction phase took place.

Methodological quality of the included studies was assessed by the Cochrane Collaboration's tool for assessing risk of bias for randomized controlled trials (RCTs) and the Newcastle-Ottawa Scale for cohort and case-control studies. Two researchers independently assessed the risk of bias, and disagreements were resolved by a third researcher if a consensus could not be reached.

Funnel plot asymmetry and Egger regression test to assess publication bias were used when at least 10 studies per outcome were included in the meta-analysis. When there are fewer studies, the power of the tests is too low to distinguish chance from real asymmetry.[15]

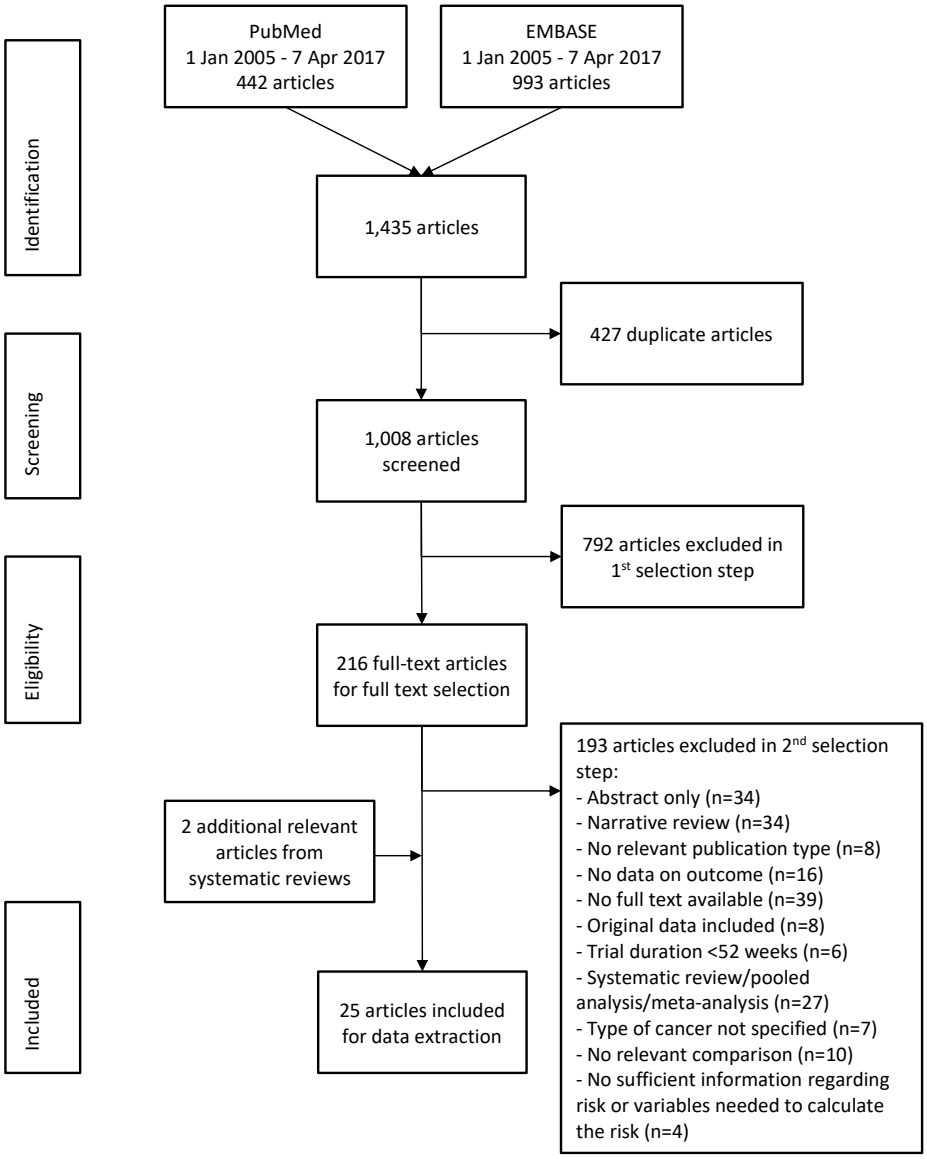


Figure 1 Flow chart of the selection procedure

Data analyses

Descriptive data were extracted and included design, first author's name, year of publication, country, study drug, comparator, sample size, mean age, % male, and follow-up. Furthermore, the number and types of cancer studied per paper were determined. We conducted meta-analyses per site-specific cancer when data (i.e., at least 1 event) from at least 2 studies were available and sufficiently homogenous (I2 < 30%). Studies with no events in both arms were excluded from the meta-analysis, because such studies do not provide any indication of either the direction or magnitude of the relative treatment effect.[16] When a study had multiple, correlated comparisons, we combined groups to create a single pair-wise comparison. When the latter was not possible, we selected the most relevant comparison. A random-effects model (Mantel-Haenszel method) was used to calculate pooled risk ratios for RCTs and pooled hazard ratios using the intention-to-treat denominator for observational studies.

As a sensitivity analyses, we also pooled the data from studies with high quality only, defined as scoring "low bias" on selective reporting for RCTs and a total score ≥8 for observational studies. Furthermore, we conducted a sensitivity analysis excluding studies which compared a DPP-4 inhibitor with a GLP-1 receptor agonist (GLP-1ra), as the mechanism of action of DPP-4 inhibitors is similar to that of GLP-1ra. If use of DPP-4 inhibitors would increase the risk of cancer, studies comparing DPP-4 inhibitors with GLP-1ra would bias the estimates.

Analyses were conducted using Review Manager Version 5.3 (RevMan; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

INDEX

Results

Study selection

Of the 1435 studies identified in the literature search in April 2017, two hundred sixteen studies remained after removing duplicates and screening titles and abstracts. The full texts of the remaining studies were evaluated for the inclusion and exclusion criteria, which resulted in a final inclusion of 25 studies.[2,3,17-39] For 4 studies, the authors were contacted, because the publications did not contain sufficient information regarding risk or variables needed to calculate the risk.[23,27,40,41] For two of them, sufficient reply was received, and these were included.[23,27] The flow chart in Figure 1 describes the stepwise selection process.

Characteristics of the included studies

Table 1 shows the characteristics of the 25 identified studies; 12 RCTs and 13 observational studies (10 cohort studies and 3 case-control studies) were included. Of the RCTs, only one study assessed cancer as the primary outcome[29] while all other RCTs had cancer as a secondary or even tertiary outcome. The observational studies reported different outcome measures (hazard ratios [n=10], odds-ratios [n=1], relative risks [n=1], and reporting odds ratios [n=1]). As the outcome of interest is rare, all the risk estimates were pooled when the same site-specific cancer was studied.

Risk of bias assessment

All of the included RCTs (n=12) were characterized by lack of information about the allocation concealment and several by lack of blinding of outcome assessment (n=9) and blinding of participants and personnel (n=6). Seven studies had a low risk of selective outcome reporting. Almost all evaluated studies had a low risk of bias according to incomplete outcome data. Eight out of 10 cohort studies and 1 out of 3 case-control studies were qualified as highest quality. Only one case-control study19 scored on the "selection" domain. Details of the quality of bias assessment are shown in Table S1 (RCTs) and S2 (observational studies).

All studies included patients with T2DM, either defined as having a diagnosis or as having a prescription for a noninsulin antidiabetic drug. Three studies performed their research in a subgroup of patients with T2DM; one in patients with T2DM and established cardiovascular disease,24 one in patients with T2DM and acute coronary syndrome,36 and one in patients with T2DM and moderate-to-severe chronic renal insufficiency.18 Follow-up across studies ranged from 52 to 156 weeks for RCTs and from 1.1 to 6.6 years for cohort studies.

Publication bias

As none of the meta-analyses included 10 or more studies, no Funnel plot asymmetry and Egger regression test were used to assess publication bias.

Risk of cancer associated with use of DPP-4 inhibitors

Among the 25 studies, 48 outcomes were described. The majority reported on pancreatic (n=12), thyroid (n=7), and colorectal (n=6) cancer. Table 2 presents the number of studies and pooled estimates for the risk of different cancer types associated with use of DPP-4 inhibitors. Figure 2 and 3 show the forest plots of the meta-analyses for RCTs and observational studies, respectively. Only the pooled estimate of the observational studies regarding breast cancer showed a statistically significant decreased risk of cancer associated with use of DPP-4 inhibitors (HR [95%CI]: 0.76 [0.60-0.96]).

Table 1 General characteristics of identified studies

#	First author[ref.]	Year	Country	DPP-4i	Comparator	Sample Size		Mean Age, y		% Male		Baseline HbA_{1c}, mmol/mol		Follow-up	
						DPP-4i	Comparator	DPP-4i	Comparator	DPP-4i	Comparator	DPP-4i	Comparator	DPP-4i	Comparator
Randomized controlled trials														(weeks)	
1	Leiter[29]	2016	Multicontinental	Saxagliptin	Placebo	8280	8212	65	65	67	67	64	64	109	
2	Schernthaner[33]	2015	Multicontinental	Saxagliptin	Glimepiride	360	360	73	73	60	63	60	60	52	
3	Green[24]	2015	Multicontinental	Sitagliptin	Placebo	7332	7339	65	66	71	71	55	55	156	
4	Schernthaner[32]	2014	Multicontinental	Linagliptin	Placebo	68	65	64	65	66	54	66	66	52	
						631	630	60	60	52	52	67	67	52	
5	Leiter[28]	2014	Multicontinental	Sitagliptin	Albiglutide	246	249	64	63	53	55	66	65	52	
6	Ahren[17]	2014	Multicontinental	Sitagliptin	Albiglutide	302	302	54	54	46	45	65	65	104	
				Sitagliptin	Glimepiride	302	307	54	54	46	52	65	65	104	
				Sitagliptin	Placebo	302	101	54	56	46	50	65	66	104	
7	Nauck[30]	2014	Multicontinental	Sitagliptin	Dulaglutide 1.5 mg	315	304	54	54	48	48	65	65	52	
				Sitagliptin	Dulaglutide 0.75 mg	315	302	54	54	48	44	65	66	52	
				Sitagliptin	Placebo	315	177	54	55	48	51	65	65	52	
8	White[36]	2013	Multicontinental	Alogliptin	Placebo	2701	2679	61	61	68	68	64	64	72	
9	Arjona Ferreira[18]	2013	Multinational	Sitagliptin	Glipizide	210	212	65	64	59	55	62	62	54	
10	Bunck[20]	2012	NL	Vildagliptin	Placebo	29	30	57	57	59	60	42	42	52	
11	Pratley[31]	2011	Multicontinental	Sitagliptin	Liraglutide 1.2 mg	219	218	55	56	55	52	69	68	52	
				Sitagliptin	Liraglutide 1.8 mg	219	221	55	55	55	52	69	68	52	
12	Kadowaki[26]	2013	Japan	Sitagliptin	Placebo	77	72	na	na	na	na	65	67	52	
Cohort studies															
1	Hicks[37]	2016	UK	DPP-4i	GLP-1ra	2422	498	68	60	0	0	nr	nr	3.5	
2	Tseng (breast)[39]	2016	Taiwan	Sitagliptin	No sitagliptin	32 436	32 436	54	54	0	0	nr	nr	1.6	2.6
3	Tseng (prostate)[38]	2016	Taiwan	Sitagliptin	No sitagliptin	37 792	37 792	52	52	100	100	nr	nr	1.6	2.5
4	Tseng (thyroid)[35]	2016	Taiwan	Sitagliptin	Other NIAD	57 659	57 659	57	57	53	53	nr	nr	1.6	2.5
5	Tseng (pancreas)[34]	2016	Taiwan	Sitagliptin	Other NIAD	71 137	933 046	53	56	54	53	nr	nr	1.6	6.6
6	Knapen[27]	2016	UK	DPP-4i	Other NIAD	22 600	182 428	58	62	56	53	Categorized		1.3	3.1
7	Htoo[25]	2016	USA	DPP-4i	TZD	46 720	28 099	76	76	37	37	nr	nr	2.0	3.3
				DPP-4i	SU	31 527	87 048	76	76	37	37	nr	nr	2.1	2.5
8	Goossens[23]	2015	UK	MET +DPP-4i	8844 SU	32 438	nr	66	nr	57	nr	77	1.2	2.5	
9	Gokhale[22]	2014	USA	DPP-4i	SU	18 179	63746	75	76	36	40	nr	nr	1.2	1.2
10	Funch[21]	2014	USA	DPP-4i	Liraglutide	40 424†	25 114†	53*	53	51*	46	nr	nr	1.3	

#	First author[ref]	Year	Country	DPP-4i	Comparator	Sample Size		Mean Age, y		% Male		Baseline HbA_{1c}, mmol/mol		Follow-up	
						DPP-4i	Comparator	DPP-4i	Comparator	DPP-4i	Comparator	DPP-4i	Comparator	DPP-4i	Comparator
Case-control studies															
1	Azoulay[19]	2016	Multicontinental	DPP-4i	SU	2726	6290	nr	nr	nr	nr	nr	nr	-	-
2	Feng[3]	2013	USA	DPP-4i	no DPP-4i	3104	3 934 676	nr	nr	nr	nr	nr	nr	-	-
3	Elashoff[2]	2011	USA	Sitagliptin	Rosiglitazone, nateglinide, repaglinide and glipizide	322	691	nr	nr	nr	nr	nr	nr	-	-
				Sitagliptin	Rosiglitazone, nateglinide, repaglinide and glipizide	308	681	nr	nr	nr	nr	nr	nr	-	-

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1ra, glucagon-like peptide-1 receptor analogues; MET, metformin; na, not available; NIAD, noninsulin antidiabetic drug; nr, not reported; SU, sulfonylureas; TZD, thiazolidinediones. *Only characteristics of entire treatment group was reported, not specifically DPP-4i users. † = person-years instead of persons.

Table 2 Effect of dipeptidyl peptidase-4 (DPP-4) inhibitor use on specific cancer types

	RCTs			Observational studies	
Type of cancer	Total	#	Pooled RR (95% CI)	#	Pooled HR (95% CI)
Pancreatic cancer	12	5*	0.55 (0.29-1.03)	7	‡
Thyroid cancer	7	5*	‡	2	1.61 (0.99-2.62)
Colorectal cancer	6	4	0.58 (0.33-1.02)	2	1.13 (0.98-1.31)
Bladder cancer**	3	2	0.65 (0.36-1.16)	1	1.33 (0.61-2.91)†
Breast cancer	5	3	0.74 (0.36-1.52)	2	0.76 (0.60-0.96)
Hematologic cancer/lymphoma/leukaemia	3	3	0.93 (0.52-1.69)	...	...
Prostate cancer	4	3	1.08 (0.71-1.64)	1	0.79 (0.61-1.04)†
Lung cancer	2	2	0.92 (0.64-1.33)	...	...
Hepatic and biliary	2	2	0.82 (0.36-1.88)	...	...
Renal	1	1	6.00 (0.25-146.68)†	...	...
Melanoma	1	1	1.35 (0.62-2.94)†	...	...
Skin	1	1	1.03 (0.75-1.40)†	...	...
Epiglottic cancer	1	1	0.67 (0.03-16.30)†	...	...
	48	33		15	

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitors; HR, hazard ratio; RCT, randomized controlled trial; RR, relative risk. *Studies with no events in both arms were excluded from the meta-analysis[16]; **One RCT included "urinary tract and bladder"; †unpooled estimate (based on 1 comparison); ‡significant heterogeneity (I^2 ≥30%).

All pooled estimates of RCTs, except prostate cancer, showed a tendency towards a decreased risk of cancer associated with the use of DPP-4 inhibitors. The two pooled estimates from observational studies, except breast cancer, showed an increased risk of cancer associated with the use of DPP-4 inhibitors, although not statistically significant.
After excluding the data from studies with "low quality", the pooled estimates from RCTs more often showed an increased risk. The results did also not alter when we excluded studies which had a GLP-1ra as the comparator group.

INDEX

Discussion

This meta-analysis shows that, based on the available limited evidence, it is not possible to conclude whether DPP-4 inhibitors were associated with an increased short-term risk of site-specific cancer compared to placebo or active antidiabetic drugs. No evidence was found for an association between DPP-4 inhibitors and an increased risk of pancreatic or thyroid cancer.
This is the first systematic review identifying and summarizing all data from human studies on the relation between use of DPP-4 inhibitors and risk of specific cancer types. In a narrative review by Tseng and colleagues[42] it was concluded that the risk of cancer remains controversial associated with DPP-4 inhibitors. Some single studies did show high statistically significant increased risks of pancreatic cancer[2,3] and probably contributed to the general idea of DPP-4 inhibitors increasing the risk of (pancreatic) cancer. It is important to keep in mind that

especially these studies used the FDA Adverse Event Reporting System database. The major limitation of this database is its incomplete data and reporting biases. Conclusions from this database are therefore hypothesis-generating and should not be used to compare adverse event rates between drugs.

The main strength of the current review is the focus on specific cancer types, as cancer can no longer be seen as one disease.[12] Another strength is its systematic approach and reporting,[43,44] although our protocol and analysis plan was not published in a recognized website.

Furthermore, by including only studies with a follow-up of at least one year, we tried to allow for an induction and latent period[45] and to minimize detection bias.[13] Six RCTs were excluded because the study duration was less than one year. Among these 6 studies, there was one study reporting one malignant neoplasm of renal pelvis,[46] one study reported one prostate cancer,[47] one study reported one gastric cancer,[48] one study reported no cancer events,[49] and two studies reported on colorectal cancer.[50,51] No statistically significant risk of colorectal cancer associated with use of DPP-4 inhibitors was found when pooling the latter two studies (relative risk [95%CI]: 0.48 [0.07-3.41]).

INDEX

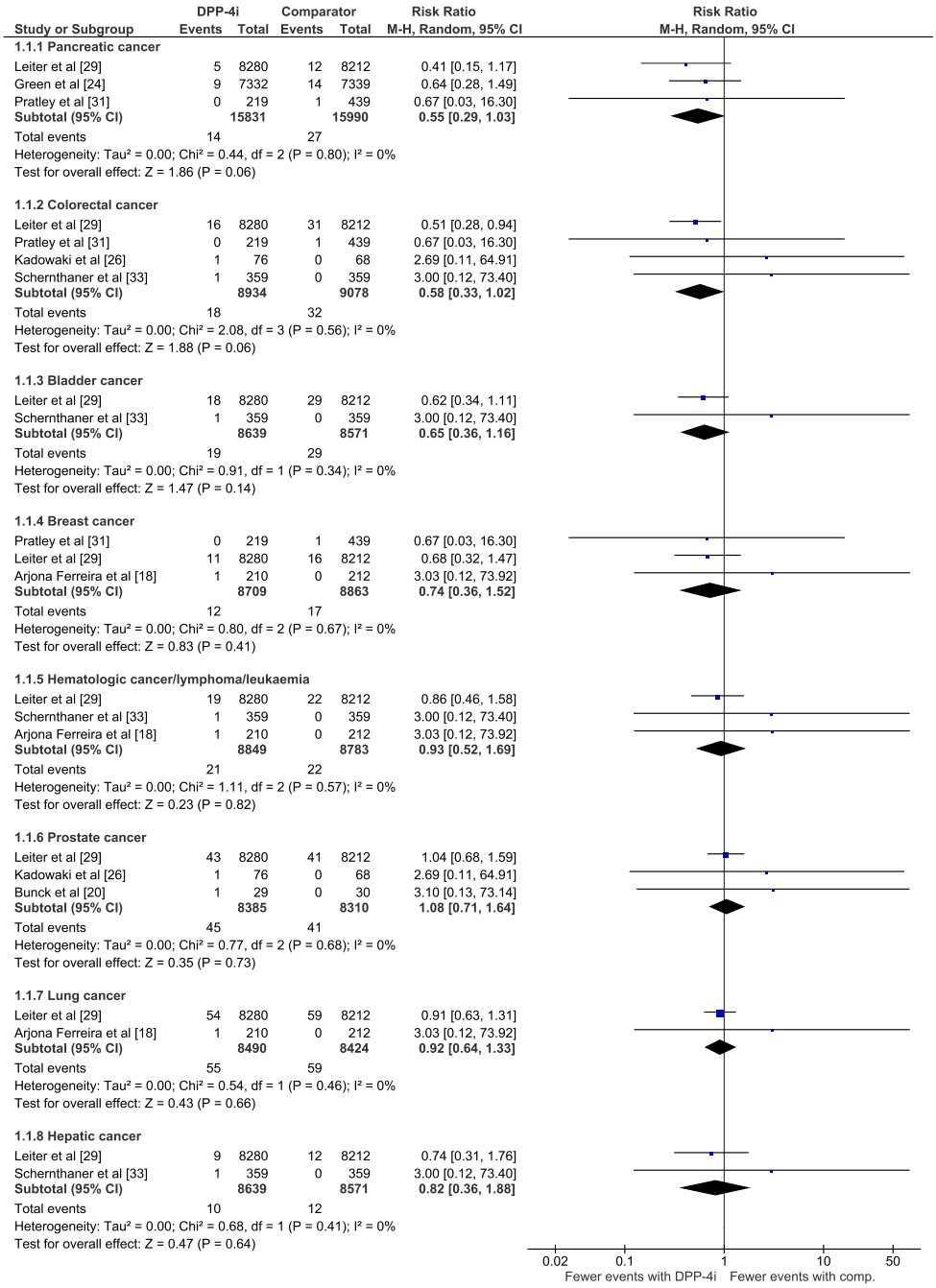


Figure 2 Effect of dipeptidyl peptidase-4 (DPP-4) inhibitor use on specific cancer - randomized controlled trials

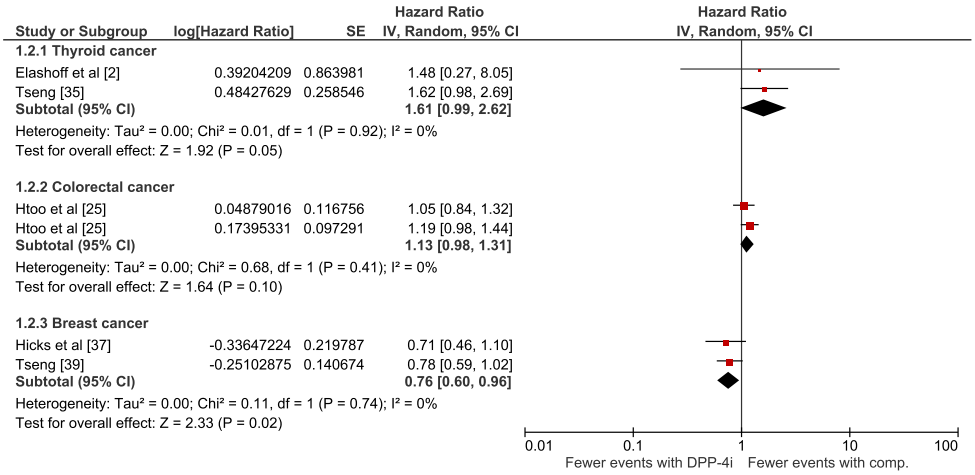


Figure 3 Effect of dipeptidyl peptidase-4 (DPP-4) inhibitor use on specific cancer - observational studies

Although we excluded studies with a follow-up of less than one year, duration of the included studies was still relatively short, which is especially important as the included follow-up is typically outweighed by clinical course of cancer. Short follow-up is likely to be an issue for the next few years since none of the clinical trials are planned for >5 years.[22] Although observational studies will not include as much exposure as RCTs, long-term safety outcomes are better captured as patients are usually longer followed in observational studies.

Furthermore, the number of relevant studies was limited. For RCTs, this is mainly because duration is usually not sufficient to study the outcome cancer, as it takes a long time to develop cancer. For observational studies, the first DPP-4 inhibitor was approved in 2006. In order to increase the sample size per meta-analysis, studies focusing on the same site-specific cancer were pooled per drug class regardless of type of DPP-4 inhibitor or comparator (i.e., any DPP-4 inhibitor versus any other noninsulin antidiabetic drug or placebo). However, this grouping can be justified as the different DPP-4 inhibitors have the same working mechanism and the risk of cancer associated with other noninsulin antidiabetic drug classes is still not proven. Our sensitivity analyses in which we (1) excluded studies with lower quality and (2) excluded studies comparing DPP-4 inhibitors to GLP-1ra, which has a similar working mechanism as DPP-4 inhibitors, did not alter the main results.

The only RCT which assessed cancer as the primary outcome[29] was a large trial and contributed a lot of weight on the pooled estimates. When excluding this RCT from the meta-analyses, the pooled risks of pancreatic and prostate cancer remained similar. The pooled risks of colorectal cancer, breast cancer and hematologic cancer/lymphoma/leukaemia shifted from a decreased to an increased risk, but still none of them were statistically significant. For the remaining outcomes (bladder cancer, lung cancer and hepatic and biliary) the number of studies remaining was too low to perform a meta-analysis.

INDEX

For our search string, we combined terms regarding cancer and DPP-4 inhibitors. Our results showed that many of the included RCTs reported cancer as a secondary or even tertiary outcome. It might therefore be expected that we have missed some studies, because they did not explicitly mention a term as defined in our search string, but might contain information relevant to the study question.
Many of the included studies tried to overcome the methodological challenges apparent when assessing the relation of medication and long-term adverse events, such as protopathic bias, confounding by indication and biases related to the inclusion of prevalent users. However, observational studies will always lack the experimental random allocation of the intervention necessary to test exposure-outcome hypotheses optimally. Most of the included RCTs, which assessed cancer as a post hoc outcome, had a short follow-up duration. Furthermore, patients included in RCTs are generally healthier compared to patients in real life and are therefore less likely to develop cancer compared to patients in real life using the studied drugs. As occurrence of cancer was not the primary objective of these RCTs, this might also have affected the reporting rate, although results derived from the sensitivity analyses by including RCTs with "low risk" of bias on selective reporting were supportive for the main analyses.
Finally, as is true with any systematic review, there is the potential for publication bias. However, given the large number of included studies with null results, the effect of publication bias on the current study was less likely.

INDEX

Conclusion

Based on the current literature, it is not possible to conclude whether DPP-4 inhibitors were associated with an increased risk of site-specific cancer. The number of included studies per cancer type was low, and many studies suffered from methodological limitations. Furthermore, the duration of the included studies was relatively short, and the effect of DPP-4 inhibitors on different cancer types remains unknown. More sound studies with long follow-up are necessary to truly assess the impact of DPP-4 inhibitors on risk of different types of cancer.

Acknowledgements

The authors would like to thank Jeppe Severens for screening titles and abstracts identified through the search strategy and for screening the full-text publications.

Conflict of interest statement

J.O., M.B., M.H., and R.H. were employees of the PHARMO Institute for Drug Outcomes Research during the conduct of this study. This independent research institute performs

financially supported studies for government and related healthcare authorities and several pharmaceutical companies. A.H. and G.N. declare no conflict of interest.
As this systematic literature review uses data from existing publications without any direct enrolment of subjects, ethical approval or informed consent is not necessary according to the Dutch law regarding human medical scientific research (Wet medisch-wetenschappelijk onderzoek met mensen [WMO]), which is enforced by the Central Committee on Research involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek, CCMO). Ethical approval for included studies in this systematic review was obtained by the responsible authors.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

INDEX

References

1. Butler PC, Elashoff M, Elashoff R, et al. A critical analysis of the clinical use of incretin-based therapies: Are the GLP-1 therapies safe? **Diabetes Care**. 2013;7:2118-2125.
2. Elashoff M, Matveyenko AV, Gier B, et al. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. **Gastroenterology**. 2011;1:150-156.
3. Feng X, Cai A, Dong K, et al. Cancer adverse events associated with dipeptidyl peptidase 4 inhibitors: Data mining of public FDA adverse event reporting system. **Pharmacotherapy**. 2012;10:e308-e309.
4. Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs--FDA and EMA assessment. **N Engl J Med**. 2014;9:794-797.
5. Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. **Diabetes Res Clin Pract**. 2012;2:271-284.
6. Chen H, Zhou X, Chen T, et al. Incretin-Based Therapy and Risk of Pancreatic Cancer in Patients with Type 2 Diabetes Mellitus: A Meta-analysis of Randomized Controlled Trials. **Diabetes Ther**. 2016;4:725-742.
7. de Heer J, Goke B. Are incretin mimetics and enhancers linked to pancreatitis and malignant transformations in pancreas? **Expert Opin Drug Saf**. 2014;11:1469-1481.
8. Suarez EA, Koro CE, Christian JB, et al. Incretin-mimetic therapies and pancreatic disease: a review of observational data. **Curr Med Res Opin**. 2014;12:2471-2481.
9. Wang H, Liu Y, Tian Q, et al. Incretin-based therapies and risk of pancreatic cancer in patients with type 2 diabetes: a meta-analysis of randomised controlled trials. **Diabetes Obes Metab**. 2017.
10. Capuano A, Sportiello L, Maiorino MI, et al. Dipeptidyl peptidase-4 inhibitors in type 2 diabetes therapy--focus on alogliptin. **Drug Des Devel Ther.** 2013;989-1001.
11. Johnson JA, Gale EA. Diabetes, insulin use, and cancer risk: are observational studies part of the solution-or part of the problem? **Diabetes**. 2010;5:1129-1131.
12. Johnson JA, Carstensen B, Witte D, et al. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. **Diabetologia**. 2012;6:1607-1618.
13. Johnson JA, Bowker SL, Richardson K, et al. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. **Diabetologia**. 2011;9:2263-2271.
14. Friberg S, Mattson S. On the growth rates of human malignant tumors: implications for medical decision making. **J Surg Oncol**. 1997;4:284-297.
15. The Cochrane Collaboration. 10.4.3.1. Recommendations on testing for funnel plot asymmetry. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions; 2011.
16. The Cochrane Collaboration. 16.9.3 Studies with no events. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions; 2011.

INDEX

17. Ahrén B, Johnson SL, Stewart M, et al. HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. **Diabetes Care**. 2014;8:2141-2148.
18. Arjona Ferreira JC, Marre M, Barzilai N, et al. Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes andmoderate-to-severe chronic renal insufficiency. **Diabetes Care**. 2013;5:1067-1073.
19. Azoulay L, Filion KB, Platt RW, et al. Incretin based drugs and the risk of pancreatic cancer: international multicentre cohort study. **Bmj**. 2016;i581.
20. Bunck MC, Poelma M, Eekhoff EM, et al. Effects of vildagliptin on postprandial markers of bone resorption and calcium homeostasis in recently diagnosed, well-controlled type 2 diabetes patients. **J Diabetes**. 2012;2:181-185.
21. Funch D, Gydesen H, Tornoe K, et al. A prospective, claims-based assessment of the risk of pancreatitis and pancreatic cancer with liraglutide compared to other antidiabetic drugs. **Diabetes Obes Metab**. 2014;3:273-275.
22. Gokhale M, Buse JB, Gray CL, et al. Dipeptidyl-peptidase-4 inhibitors and pancreatic cancer: a cohort study. **Diabetes Obes Metab**. 2014;12:1247-1256.
23. Goossens ME, Buntinx F, Zeegers MP, et al. Influence of metformin intake on the risk of bladder cancer in type 2 diabetes patients. **Br J Clin Pharmacol**. 2015;6:1464-1472.
24. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. **N Engl J Med**. 2015;3:232-242.
25. Htoo PT, Buse JB, Gokhale M, et al. Effect of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors on colorectal cancer incidence and its precursors. **Eur J Clin Pharmacol**. 2016.
26. Kadowaki T, Tajima N, Odawara M, et al. Addition of sitagliptin to ongoing metformin monotherapy improves glycemic control in Japanese patients with type 2 diabetes over 52weeks. **Journal of Diabetes Investigation**. 2013;2:174-181.
27. Knapen LM, van Dalem J, Keulemans YC, et al. Use of incretin agents and risk of pancreatic cancer: a population-based cohort study. **Diabetes Obes Metab**. 2016;3:258-265.
28. Leiter LA, Carr MC, Stewart M, et al. Efficacy and safety of the once-weekly GLP-1 receptor agonist albiglutide versus sitagliptin in patients with type 2 diabetes and renal impairment: A randomized phase III study. **Diabetes Care**. 2014;10:2723-2730.
29. Leiter LA, Teoh H, Mosenzon O, et al. Frequency of cancer events with saxagliptin in the SAVOR-TIMI 53 trial. **Diabetes Obes Metab**. 2016;2:186-190.
30. Nauck M, Weinstock RS, Umpierrez GE, et al. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). **Diabetes Care**. 2014;8:2149-2158.
31. Pratley R, Nauck M, Bailey T, et al. One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: A randomised, parallel-group, open-label trial. **International Journal of Clinical Practice**. 2011;4:397-407.

32. Schernthaner G, Barnett AH, Patel S, et al. Safety and efficacy of the dipeptidyl peptidase-4 inhibitor linagliptin in elderly patients with type 2 diabetes: A comprehensive analysis of data from 1331 individuals aged≥65years. **Diabetes, Obesity and Metabolism**. 2014;11:1078-1086.
33. Schernthaner G, Durán-Garcia S, Hanefeld M, et al. Efficacy and tolerability of saxagliptin compared with glimepiride in elderly patients with type 2 diabetes: A randomized, controlled study (GENERATION). **Diabetes, Obesity and Metabolism**. 2015;7:630-638.
34. Tseng CH. Sitagliptin and pancreatic cancer risk in patients with type 2 diabetes. **Eur J Clin Invest**. 2016;1:70-79.
35. Tseng CH. Sitagliptin use and thyroid cancer risk in patients with type 2 diabetes. **Oncotarget**. 2016.
36. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. **N Engl J Med**. 2013;14:1327-1335.
37. Hicks BM, Yin H, Yu OH, et al. Glucagon-like peptide-1 analogues and risk of breast cancer in women with type 2 diabetes: population based cohort study using the UK Clinical Practice Research Datalink. **Bmj**. 2016;i5340.
38. Tseng CH. Sitagliptin may reduce prostate cancer risk in male patients with type 2 diabetes. **Oncotarget**. 2016.
39. Tseng CH. Sitagliptin May Reduce Breast Cancer Risk in Women With Type 2 Diabetes. **Clin Breast Cancer**. 2016.
40. Narushima D, Kawasaki Y, Takamatsu S, et al. Adverse events associated with incretin-based drugs in Japanese spontaneous reports: A mixed effects logistic regression model. **PeerJ**. 2016;3.
41. Montilla S, Marchesini G, Sammarco A, et al. Drug utilization, safety, and effectiveness of exenatide, sitagliptin, and vildagliptin for type 2 diabetes in the real world: Data from the Italian AIFA Anti-diabetics Monitoring Registry. **Nutrition, Metabolism and Cardiovascular Diseases**. 2014;12:1346-1353.
42. Tseng CH, Lee KY, Tseng FH. An updated review on cancer risk associated with incretin mimetics and enhancers. **J Environ Sci Health C Environ Carcinog Ecotoxicol Rev**. 2015;1:67-124.
43. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. **Int J Surg**. 2010;5:336-341.
44. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. **JAMA**. 2000;15:2008-2012.
45. Rothman KJ. Induction and latent periods. **Am J Epidemiol**. 1981;2:253-259.
46. Seino Y, Hiroi S, Hirayama M, et al. Efficacy and safety of alogliptin added to sulfonylurea in Japanese patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial with an open-label, long-term extension study. **Journal of Diabetes Investigation**. 2012;6:517-525.

47. Aschner P, Chan J, Owens DR, et al. Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): A multicentre, randomised open-label trial. **The Lancet**. 2012;9833:2262-2269.
48. Kikuchi M, Abe N, Kato M, et al. Vildagliptin dose-dependently improves glycemic control in Japanese patients with type 2 diabetes mellitus. **Diabetes Research and Clinical Practice**. 2009;2:233-240.
49. Chen Y, Ning G, Wang C, et al. Efficacy and safety of linagliptin monotherapy in Asian patients with inadequately controlled type 2 diabetes mellitus: A multinational, 24-week, randomized, clinical trial. **Journal of Diabetes Investigation**. 2015;6:692-698.
50. Bajaj M, Gilman R, Patel S, et al. Linagliptin improved glycaemic control without weight gain or hypoglycaemia in patients with Type 2 diabetes inadequately controlled by a combination of metformin and pioglitazone: A 24-week randomized, double-blind study. **Diabetic Medicine**. 2014;12:1505-1514.
51. Barnett AH, Patel S, Harper R, et al. Linagliptin monotherapy in type 2 diabetes patients for w hom metformin is inappropriate: An 18-week randomized, double-blind, placebo-controlled phase III trial with a 34-week active-controlled extension. **Diabetes, Obesity and Metabolism**. 2012;12:1145-1154.

INDEX

Supporting Information

Data S1 Search string

PubMed

1. Neoplasms [MeSH] OR cancer*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR neoplas*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR oncolog*[tiab] OR malignan*[tiab] OR metasta*[tiab]
2. gliptin*[tiab] OR "dipeptidyl peptidase 4"[tiab] OR "DPP 4"[tiab] OR DPP4[tiab] OR "dipeptidyl peptidase IV"[tiab] OR "DPP IV"[tiab] OR linagliptin[tiab] OR "BI 1356"[tiab] OR "BS 1356"[tiab] OR saxagliptin[tiab] OR "BMS 477118"[tiab] OR sitagliptin[tiab] OR "MK 0431"[tiab] OR vildagliptin[tiab] OR "LAF 237"[tiab] OR LAF237[tiab] OR alogliptin[tiab] OR "SYR 322"[tiab] OR SYR322[tiab] OR anagliptin[tiab] OR bisegliptin[tiab] OR carmegliptin[tiab] OR R1579[tiab] OR RO4876904[tiab] OR denagliptin[tiab] OR "GW 823093"[tiab] OR GW823093[tiab] OR dutogliptin[tiab] OR PHX1149[tiab] OR evogliptin[tiab] OR "DA 1229"[tiab] OR gemigliptin[tiab] OR "LC15 0444"[tiab] OR gosogliptin[tiab] OR "PF 00734200"[tiab] OR "PF 734200"[tiab] OR melogliptin[tiab] OR "GRC 200"[tiab] OR omarigliptin[tiab] OR "MK 3102"[tiab] OR teneligliptin[tiab] OR trelagliptin[tiab] OR "SYR 472"[tiab]
3. #1 AND #2

EMBASE

1. 'neoplasm'/exp OR cancer*:ab,ti OR tumor*:ab,ti OR tumour*:ab,ti OR neoplas*:ab,ti OR carcinoma*:ab,ti OR adenocarcinoma*:ab,ti OR oncolog*:ab,ti OR malignan*:ab,ti OR metasta*:ab,ti
2. gliptin*:ab,ti OR (dipeptidyl:ab,ti AND peptidase:ab,ti AND 4:ab,ti) OR (dpp:ab,ti AND 4:ab,ti) OR dpp4:ab,ti OR (dipeptidyl:ab,ti AND peptidase:ab,ti AND iv:ab,ti) OR (dpp:ab,ti AND iv:ab,ti) OR linagliptin:ab,ti OR (bi:ab,ti AND 1356:ab,ti) OR (bs:ab,ti AND 1356:ab,ti) OR saxagliptin:ab,ti OR (bms:ab,ti AND 477118:ab,ti) OR sitagliptin:ab,ti OR (mk:ab,ti AND 0431:ab,ti) OR vildagliptin:ab,ti OR (laf:ab,ti AND 237:ab,ti) OR laf237:ab,ti OR alogliptin:ab,ti OR (syr:ab,ti AND 322:ab,ti) OR syr322:ab,ti OR anagliptin:ab,ti OR bisegliptin:ab,ti OR carmegliptin:ab,ti OR r1579:ab,ti OR ro4876904:ab,ti OR denagliptin:ab,ti OR (gw:ab,ti AND 823093:ab,ti) OR gw823093:ab,ti OR dutogliptin:ab,ti OR phx1149:ab,ti OR evogliptin:ab,ti OR (da:ab,ti AND 1229:ab,ti) OR gemigliptin:ab,ti OR (lc15:ab,ti AND 0444:ab,ti) OR gosogliptin:ab,ti OR (pf:ab,ti AND 00734200:ab,ti) OR (pf:ab,ti AND 734200:ab,ti) OR melogliptin:ab,ti OR (grc:ab,ti AND 8200:ab,ti) OR omarigliptin:ab,ti OR (mk:ab,ti AND 3102:ab,ti) OR teneligliptin:ab,ti OR trelagliptin:ab,ti OR (syr:ab,ti AND 472:ab,ti)
3. #1 AND #2

INDEX

Table S1 Quality of bias assessment of the included studies according to the Cochrane Collaboration's tool

	Random sequence generation	Allocation concealment	Selective reporting	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Other bias
Leiter[29]	L	U	H	L	U	L	L
Schernthaner[33]	L	U	L	H	U	L	L
Green[24]	L	U	H	L	L	L	L
Schernthaner[32]	U	U	L	U	U	L	L
Leiter[28]	L	U	H	L	L	H	L
Ahrén[17]	U	U	L	L	L	L	L
Nauck[30]	L	U	H	U	U	L	L
White[36]	U	U	U	U	U	L	L
Arjona Ferreira[18]	L	U	L	L	U	L	L
Bunck[20]	U	U	U	U	U	U	L
Pratley[31]	L	U	L	H	H	L	L
Kadowaki[26]	L	U	L	U	U	L	L

L = low risk of bias; H = high risk of bias; U = unclear risk of bias.

Table S2 Quality of bias assessment of the included studies according to the Newcastle-Ottawa Scale

Cohort studies	Total	Selection Represen-tativeness	Selection non exposed	Ascertain-ment exposure	Outcome not present at start	Comparability Adjusted for age	Adjusted for another factor	Outcome Assess-ment	Length of follow-up	Adequacy of follow-up
Hicks[37]	9	1	1	1	1	1	1	1	1	1
Tseng (breast)[39]	9	1	1	1	1	1	1	1	1	1
Tseng (prostate)[38]	9	1	1	1	1	1	1	1	1	1
Tseng (thyroid)[35]	9	1	1	1	1	1	1	1	1	1
Tseng (pancreas)[34]	8	1	1	1	1	1	1	1	1	…
Knapen[27]	9	1	1	1	1	1	1	1	1	1
Htoo[25]	8	1	1	…	1	1	1	1	1	1
Goossens[23]	8	…	1	1	1	1	1	1	1	1
Gokhale[22]	7	1	1	…	1	1	1	1	…	1
Funch[21]	7	…	1	1	1	1	1	1	…	1

Case-control studies	Total	Selection Case definition	Represent-ativeness	Selection controls	Definition controls	Comparability Adjusted for age	Adjusted for another factor	Ascer-tainment	Exposure Same ascer-tainment method for cases and controls	Non-response rate
Azoulay[19]	9	1	1	1	1	1	1	1	1	1
Feng[3]	1	…	…	…	…	…	…	…	1	…
Elashoff[2]	2	…	…	…	…	1	…	…	1	…

INDEX

CHAPTER 7

Type 2 diabetes, but not insulin (analogue) treatment, is associated with more advanced stages of breast cancer: a national linkage of cancer and pharmacy registries

Jetty A. Overbeek, Myrthe P.P. van Herk-Sukel, Pauline A.J. Vissers, Amber A.W.A. van der Heijden, Heleen K. Bronsveld, Ron M.C. Herings, Marjanka K. Schmidt, Giel Nijpels

Diabetes Care. 2019 Jan 24. pii: dc182146. doi: 10.2337/dc18-2146. [Epub ahead of print]

Abstract

Objective: To investigate whether women with type 2 diabetes (T2D) develop a more advanced stage of breast cancer and whether treatment with insulin (analogues) is associated with the development of specific breast cancer characteristics.

Research Design and Methods: For this nested case-control study, women with breast cancer diagnosed in 2002-2014 were selected from the linked Netherlands Cancer Registry-PHARMO Database Network (N = 33,377). T2D was defined as receiving two or more dispensings of noninsulin blood glucose lowering drugs prior to breast cancer diagnosis. Women with T2D were matched to women without diabetes. Among women with T2D, insulin users and nonusers were compared. Multivariable ordinal logistic regression was used to investigate the association between T2D/insulin and breast cancer characteristics, including TNM classification (tumour size, lymph node status, metastasis), morphology, grade, oestrogen and progesterone receptor (PR), human epidermal growth factor receptor 2, and molecular subtype.

Results: Women with T2D (n=1,567) were more often diagnosed with a more advanced tumour stage (odds ratio [95%CI]: 1.28 [1.13-1.44]) and a higher grade (1.22 [1.08-1.39]), though less often with a PR-negative breast tumour (0.77 [0.67-0.89]) than women without DM (n=6,267). No associations were found for the other breast cancer characteristics. Women with T2D using insulin (n=388) were not diagnosed with different breast cancer characteristics compared to women with T2D not using insulin (n=1,179).

Conclusions: Our study suggests that women with T2D are at increased risk to be diagnosed with a more aggressive type of breast cancer than women without diabetes. No evidence was found that the use of insulin (analogues) is associated with developing more advanced breast cancer tumours.

INDEX

Introduction

The prevalence of diabetes is increasing worldwide.[1] Women with type 2 diabetes (T2D) are at increased risk to develop breast cancer,[2] which is the most common malignant tumour in females.[3] In the Netherlands, the incidence of breast cancer increased with 65% between 1989 and 2017.[4, 5] Furthermore, mortality after breast cancer is 50% higher among women with diabetes compared to women without diabetes, including after correcting for tumour stage.[6]

Several mechanisms have been suggested for the increased risk of breast cancer among women with T2D, such as common risk factors like obesity,[7] the specific metabolic derangements of diabetes itself (i.e., hyperglycaemia,[8] hyperinsulinemia, and insulin resistance), and the use of insulin and specifically insulin analogues.[9-11] Hyperinsulinemia in itself, especially present in people with impaired glucose tolerance, may promote tumour cell growth directly via insulin receptors or indirectly via the insulin-like growth factor-1 (IGF-1) receptor.[12] IGF-1, and subsequently the IGF-1 receptor, could act as a growth stimulus for tumour cells and increase tumour growth, invasion, and metastasis.[13] In comparison with counterparts without diabetes, patients with breast cancer and diabetes tend to present at later stages.[14] However, it is yet unclear what the pathophysiologic interactions between diabetes and breast cancer are and whether improvements in diabetes care can reduce the increased mortality in patients with breast cancer.[14] Whether the use of insulin (analogues) is associated with this risk is still uncertain. A large population-based cohort study concluded that long-term use of insulin glargine was associated with an increased risk of breast cancer in women with T2D compared to Neutral Protamine Hagedorn (NPH) insulin.[15] However, a recent systematic review[16] and a five-country cohort study[17] concluded that insulin (analogue) treatment does not impact the risk of breast cancer among women with diabetes compared to women without diabetes. Whether T2D or the use of insulin (analogues) increases the risk of developing a more aggressive or less treatment-responsive tumour is hardly well studied, since most studies lacked detailed tumour or use-of-insulin (analogues) data. Furthermore, the majority of these studies suffered from methodological limitations or lacked power. In the current study, a comprehensive large database with detailed data was used, creating the opportunity to study the association between T2D and breast cancer characteristics. Also, the effect of insulin (analogues) use on breast cancer characteristics was studied among women with T2D.

INDEX

Research Design and Methods

Data sources

For the current study, data were obtained from the Netherlands Cancer Registry (NCR) and the PHARMO Database Network. The NCR is maintained by the Netherlands Comprehensive Cancer Organisation (IKNL)[18] and is notified for new patients with cancer by pathology departments, general hospitals, and radiotherapy institutes. Key information in the NCR includes cancer diagnosis, tumour staging, tumour site and morphology, and primary cancer treatment. Staging of cancer is categorised according to the TNM classification (tumour size, lymph node status, metastasis) developed and maintained by the Union for International Cancer Control. Tumours are classified based on site (topography) and morphology (histology), according to the World Health Organization International Classification of Diseases for Oncology (ICD-O-3).

The PHARMO Database Network is a population-based network of electronic health care databases containing data from both primary and secondary health care settings in the Netherlands. The Out-patient Pharmacy Database of the PHARMO Database Network was used to select women with T2D and to obtain detailed data on the exposure to insulin. The Out-patient Pharmacy Database comprises general practitioner- or specialist- prescribed health care products dispensed by the out-patient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty, and costs. Drug dispensings are coded according to the World Health Organization Anatomical Therapeutic Chemical (ATC) Classification System. Outpatient pharmacy data cover a catchment area representing 3.6 million residents. The Hospitalisation Database and the Clinical Laboratory Database of the PHARMO Database Network were used to characterise women in terms of comorbidities.

The privacy committees of the PHARMO Institute for Drug Outcomes Research and the NCR approved this study.

INDEX

Study design

A nested case-control study in a retrospective breast cancer cohort was performed. Women with breast cancer and T2D were matched and compared with women with breast cancer without diabetes. Furthermore, women with T2D using insulin (analogues) were compared with women with T2D not using insulin (analogues) (unmatched). Per breast cancer characteristic, case subjects were defined as women diagnosed with a more aggressive/less treatment-responsive outcome. Control subjects were defined as women experiencing a less aggressive/more treatment-responsive outcome.

Study population

The source population included all women diagnosed with an invasive breast cancer diagnosis (ICD-O-3: C50.x, stage I-IV) between 2002 and 2014 who were registered in the NCR Out-patient Pharmacy Database from the PHARMO Database Network). The date of

the first diagnosis with invasive breast cancer was defined as the index date. For assessment of exposure in the 4 years prior to index date, all selected women needed to have at least 4 years of continuous enrolment in the PHARMO Database Network prior to the index date. Furthermore, women who underwent oophorectomy at any time prior to the index date were excluded.

Women receiving two or more dispensings of noninsulin blood glucose lowering drugs (NIBGLDs) (ATC code A10B) in the 4 year prior to their index date were defined as women with T2D. At least two dispensings of NIBGLD had to be dispensed within 6 months. Women with type 1 diabetes, defined as receiving insulin (analogues) (ATC code A10A) and no NIBGLDs in the 4 year prior to index date, were excluded. Each woman with T2D was matched to up to four women without diabetes (no dispensing for drugs used to treat diabetes [ATC code A10]) on age at index date (± 2 years). Control subjects had to be alive on the index date of their matched case subject and could not be matched more than once. Among women with T2D, women with a dispensing of insulin in the 4-year period prior to the index date were defined as insulin users.

Patient characteristics

For all women included, the following general characteristics were determined at index date: age, year of index, and socioeconomic status (SES). SES was derived from Statistics Netherlands, which based SES on salary per four-digit zip code. Furthermore, comedication (use of statins, antihypertensive drugs, glucocorticoids, oestrogen-progestogen contraceptives, hormone-replacement therapy [HRT] in the year prior to index date) and comorbidities (renal failure, retinopathy, hypertension, stroke, congestive heart failure, ischaemic heart disease, peripheral artery disease, cerebrovascular disease in the entire available history) were determined for characterisation of patients. Comorbidities were based on hospitalisations, and renal failure was defined as having two or more estimated glomerular filtration rate measurements <60 mL/min/1.73 m^2 90-365 days apart. Furthermore, an updated chronic disease score (CDS) was calculated. This score was based on the use of specific classes of medications in the year prior to index date (see Supplementary Table 1). The CDS has been shown to be a valid measure of complications related to an individual patient's burden of chronic somatic diseases and is clearly associated with a fivefold increase in risk of hospitalisation and a 10-fold increase in risk of dying.[19]

Exposure of insulin (analogues)

Duration of use

The cumulative days of exposure in the 4 years prior to index date were calculated for each patient by converting dispensings into treatment episodes of uninterrupted use. As the dosing regimen is hardly ever registered with insulin, the duration of insulin was based on the legal limit of the maximal duration (90 days). In case of an interruption between two dispensings, use of insulin or NIBGLD was considered interrupted if the duration of this gap was less than half the period of the given dispensing, according to the method of Catalan and LeLorier.[20]

Dose
As insulin dose descriptions are hardly ever registered in the Out-patient Pharmacy Database, dose estimations relied on dispensed amounts of insulin over time. Per woman, the average daily dose was calculated as the sum of all dispensed doses during the insulin episodes in the 4 years prior to index date, divided by the cumulative days of exposure for insulin in the 4 years prior to index date.

Insulin analogues versus human insulin
Use of human insulin (ATC code A10AB01, A10AC01, A10AD01, and A10AE01) and use of insulin analogues (ATC code A10A, excluding A10AB01, A10AC01, A10AD01, and A10AE01) in the 4 years prior to index date was determined. The number of women using human insulin only, insulin analogue only, or both human and insulin analogues were presented.

Breast cancer characteristics
The following breast cancer characteristics at index date were studied as outcomes, based on the available information in the NCR data: tumour size (T in "TNM" classification), lymph node status (N in TNM classification), distant metastasis (M in TNM-classification), stage (I-IV), morphology (ductal, lobular, mixed, other), histological tumour grade (grade 1 [well differentiated], grade 2 [moderately differentiated], grade 3 [poorly differentiated]), hormone receptor status (oestrogen receptor [ER] and progesterone receptor [PR]), human epidermal growth factor receptor 2 (HER2), and molecular subtypes. Surrogate definitions of molecular subtypes were used and based on the immunohistochemical measurement of the (hormone) receptors. Based on the surrogate definitions described by the St Gallen International Expert Panel,[21] the following subtypes were defined: luminal A, luminal B, nonluminal (HER2 positive), and triple negative (see Table 1). As Ki-67 measurement was not available, grade was used to distinguish between luminal A and luminal B.[21]

INDEX

Molecular subtype is associated with different short-term clinical outcome and prognosis. Luminal tumours have the best prognosis compared to nonluminal (HER2 positive) and triple negative tumours.

Table 1 Surrogate definitions of molecular subtypes of breast cancer

Molecular subtype	Clinico-pathologic definition
Luminal A	ER+ and/or PR+, HER2-, and grade 1 or 2
Luminal B	ER+ and/or PR+, HER2-, and grade 3
	ER+ and/or PR+, HER2+
Nonluminal (HER2 positive)	ER-, PR-, and HER2+
Triple negative	ER-, PR-, and HER2-

Surrogate definitions of molecular subtypes of breast cancer are from Goldhirsch et al.[21]

Statistical analyses

The χ^2 test was used to assess whether categorical characteristics (excluding "unknown") differed 1) between women with breast cancer with T2D and women with breast cancer without diabetes and 2) among women with breast cancer with T2D: women using insulin (analogues) and women not using insulin (analogues). For continuous characteristics, ANOVA was used.

As most of the breast cancer characteristics in this study are ordinal, categorised with two or more categories, multivariable ordinal logistic regression was used to investigate the two associations: 1) T2D and breast cancer characteristics and 2) insulin (analogue) treatment and breast cancer characteristics. Separate models were constructed for each exposure (T2D or insulin [analogues]) to evaluate each breast cancer characteristic. Odds ratios (ORs) and their corresponding 95% CI were adjusted for age, year of index date, SES, CDS, and use of glucocorticoids, oestrogen-progestogen contraceptives, and HRT in the year prior to index date and presented for the different breast cancer characteristics. For the comparison between insulin (analogues) versus no insulin (analogues) and breast cancer among women with T2D, ORs were also adjusted for duration of diabetes. Comparisons regarding duration and dose of insulin (analogues) were performed among women with T2D who used insulin (analogues) and adjusted for duration of diabetes, age, CDS, and patient characteristics that statistically significant differed between the two groups ($p<.05$). ORs >1 indicate that exposed women are more likely to be diagnosed with a worse outcome (see Table 3 for the order from good to worse outcome of each breast cancer characteristic).

Based on the median duration of insulin use, durations for women's insulin use were characterised as "short" (i.e., shorter use than the median duration 3.4 years) or "long" (i.e., same or longer use than the median duration). The same was done for the dose of insulin (median dose was 41.1 international units [IU]). Based on the median dose, women were characterised as "low" and "high".

All data were prepared and analysed using SAS programs organized within SAS Enterprise Guide, version 4.3 (SAS Institute Inc., Cary, NC), and conducted under Windows using SAS, version 9.2.

Subgroup analysis

As insulin analogues have binding affinities and activities to the IGF-1 receptor different from those human insulin has, we performed a subgroup analysis among women with breast cancer and T2D using human insulin only versus women with breast cancer and T2D using insulin analogues only. As the number of women in these groups is expected to be low, ORs and their corresponding CIs were only adjusted for patient characteristics that statistically significant differed between the two groups ($p<.05$), except for year of index date. As insulin analogues were marketed later than human insulin, this characteristic differs between these groups by definition.

Results

Study population

Supplementary Fig. 1 shows the flowchart of patient selection; 1,567 women with T2D were matched to 6,267 women without diabetes. Approximately one quarter of the women with T2D used insulin in the 4 years prior to the index date (n=388).

Table 2 Patient characteristics of women with breast cancer, stratified by no diabetes/T2D and by insulin use among women with T2D

	Women without diabetes: total N = 6,267	Women with T2D			T2D vs. no diabetes p-value	Insulin vs. no insulin p-value
		Total N = 1,567	Insulin N = 388	No insulin N = 1,179		
Age (years)					0.80	0.19
≤53	330 (5)	85 (5)	16 (4)	69 (6)		
>53	5,937 (95)	1,482 (95)	372 (96)	1,110 (94)		
Mean ± SD	71 ± 11	71 ± 11	70 ± 10	71 ± 11		
Year of index date					<.0001	0.27
2002-2005	2,129 (34)	210 (13)	44 (11)	166 (14)		
2006-2008	1,464 (23)	253 (16)	57 (15)	196 (17)		
2009-2011	1,558 (25)	477 (30)	118 (30)	359 (30)		
2012-2014	1,116 (18)	627 (40)	169 (44)	458 (39)		
SES					<.05	0.05
high	1,983 (32)	437 (28)	88 (23)	349 (30)		
middle	1,995 (32)	529 (34)	136 (35)	393 (33)		
low	2,262 (36)	596 (38)	162 (42)	434 (37)		
unknown	27 (<0.5)	5 (<0.5)	2 (1)	3 (<0.5)		
Comedication						
statins	1,043 (17)	970 (62)	262 (68)	708 (60)	<.0001	<.01
antihypertensive drugs	2,675 (43)	1,238 (79)	329 (85)	909 (77)	<.0001	<.01
glucocorticoids	420 (7)	158 (10)	51 (13)	107 (9)	<.0001	<.05
ER-PR contraceptives	128 (2)	28 (2)	7 (2)	21 (2)	0.52	0.98
HRT	503 (8)	88 (6)	14 (4)	74 (6)	<.01	<.05
Comorbidities						
renal failure	233 (4)	140 (9)	54 (14)	86 (7)	<.0001	<.0001
retinopathy	12 (<0.5)	13 (1)	6 (2)	7 (1)	<.0001	0.07
hypertension	284 (5)	166 (11)	53 (14)	113 (10)	<.0001	<.05
stroke	109 (2)	36 (2)	13 (3)	23 (2)	0.14	0.11
CHF	143 (2)	84 (5)	38 (10)	46 (4)	<.0001	<.0001
IHD	333 (5)	157 (10)	61 (16)	96 (8)	<.0001	<.0001
PAD	105 (2)	46 (3)	16 (4)	30 (3)	<.01	0.11
cerebrovascular disease	207 (3)	72 (5)	24 (6)	48 (4)	<.05	0.08
CDS					<.0001	<.0001
<7	5,049 (81)	725 (46)	145 (37)	580 (49)		
≥7	1,218 (19)	842 (54)	243 (63)	599 (51)		
Duration of diabetes (years)					n.a.	<.0001
<1	-	107 (7)	0 (0)	107 (9)		
1-<2	-	140 (9)	5 (1)	135 (11)		
2-<5	-	369 (24)	32 (8)	337 (29)		
≥5	-	804 (51)	310 (80)	494 (42)		
unknown	-	147 (9)	41 (11)	106 (9)		

Data are n (%) unless otherwise indicated. CHF, congestive heart failure; IHD, ischaemic heart disease; n.a., not applicable; PAD, peripheral artery disease.

Patient characteristics

The patient characteristics for women with breast cancer are shown in Table 2, stratified by no diabetes/T2D and by insulin use among women with T2D. Mean age at index date (e.g., first diagnosis of breast cancer diagnosis) was ~71 years. Women with T2D had a slightly lower SES than women without diabetes and, among women with T2D, women using insulin had a lower SES than women not using insulin. Furthermore, use of statins, antihypertensives, and glucocorticosteroids was the highest among women with T2D using insulin, followed by women with T2D not using insulin. A similar pattern was observed for the selected comorbidities and the CDS. The Dutch diabetes guideline advices to determine the indication for an antihypertensive drug and a statin among people with diabetes, explaining the higher proportion of users among women with diabetes. Use of HRT was the highest among women without diabetes (8%) and differed significantly from the use among women with T2D (6%). The same was true among women using insulin (6%) versus women not using insulin (4%) ($p<.05$). In general, these results show that women with T2D using insulin had the highest disease severity, followed by women with T2D not using insulin.

Exposure

Among women with T2D using insulin (analogues) (N = 388), median insulin duration was 3.4 years (interquartile range 1.7-4.0) with an average daily dose of 41.1 IU (23.2-68.6). More than half of the women using insulin only used insulin analogues (n = 236 [61%]) and 15% (n = 59) only used human insulin in the 4 years prior to index date.

Use of NIBGLD was 88% among women with T2D using insulin and 97% among women with T2D not using insulin. Among all, the most commonly used NIBGLD class was metformin, followed by sulfonylurea derivatives.

Breast cancer characteristics

Table 3 presents the breast cancer characteristics of women with breast cancer, stratified by no diabetes/T2D and by insulin use among women with T2D.

Women with T2D tended to have a larger tumour ($p<.01$), more lymph nodes affected ($p<.05$), a more advanced tumour stage ($p<.01$) and grade ($p<.05$), and a different distribution in morphology ($p<.05$), and less often a PR-negative breast tumour ($p<.0001$). Among women with T2D, distribution of breast cancer characteristics did not differ between women using insulin (analogues) and women not using insulin (analogues).

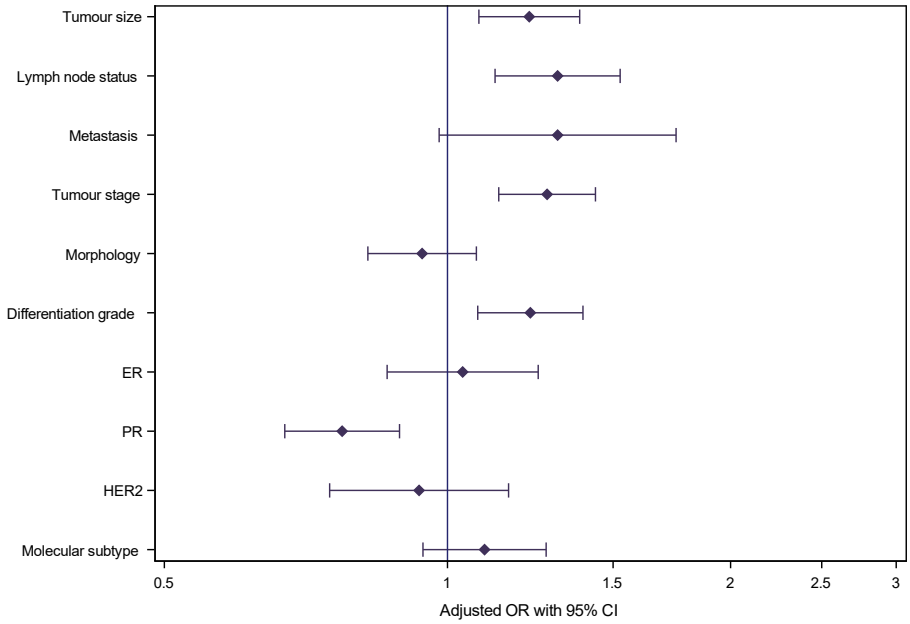
Table 3 Breast cancer characteristics of women with breast cancer, stratified by no diabetes/T2D and by insulin use among women with T2D

	Women without diabetes: total N = 6,267	Women with T2D			T2D vs. no diabetes p-value	Insulin vs. no insulin p-value
		Total N = 1,567	Insulin N = 388	No insulin N = 1,179		
TNM classification						
Tumour size					<.01	0.67
1	3,439 (55)	799 (51)	192 (49)	607 (51)		
2	1,859 (30)	505 (32)	122 (31)	383 (32)		
3	204 (3)	69 (4)	17 (4)	52 (4)		
4	319 (5)	94 (6)	28 (7)	66 (6)		
unknown	446 (7)	100 (6)	29 (7)	71 (6)		
Lymph node status					<.05	0.74
0	4,891 (78)	1,194 (76)	298 (77)	896 (76)		
1	974 (16)	287 (18)	78 (20)	209 (18)		
2	37 (1)	14 (1)	3 (1)	11 (1)		
3	48 (1)	17 (1)	3 (1)	14 (1)		
unknown	317 (5)	55 (4)	6 (2)	49 (4)		
Metastasis					0.06	0.18
0	6,024 (96)	1,490 (95)	364 (94)	1,126 (96)		
1	243 (4)	77 (5)	24 (6)	53 (4)		
Stage					<.01	0.53
I	3,412 (54)	771 (49)	186 (48)	585 (50)		
II	2,216 (35)	613 (39)	150 (39)	463 (39)		
III	345 (6)	99 (6)	27 (7)	72 (6)		
IV	243 (4)	77 (5)	24 (6)	53 (4)		
unknown	51 (1)	7 (<0.5)	1 (<0.5)	6 (1)		
Morphology					<.05	0.74
ductal	4,385 (70)	1,149 (73)	289 (74)	860 (73)		
lobular	841 (13)	187 (12)	45 (12)	142 (12)		
ductal-lobular mixed	376 (6)	72 (5)	14 (4)	58 (5)		
other	665 (11)	159 (10)	40 (10)	119 (10)		
Grade					<.05	0.63
grade 1	1,401 (22)	308 (20)	72 (19)	236 (20)		
grade 2	2,423 (39)	581 (37)	138 (36)	443 (38)		
grade 3	1,264 (20)	355 (23)	93 (24)	262 (22)		
unknown	1,179 (19)	323 (21)	85 (22)	238 (20)		
Hormone receptor status						
ER					0.94	0.97
positive	4,671 (75)	1,276 (81)	316 (81)	960 (81)		
negative	760 (12)	209 (13)	52 (13)	157 (13)		
unknown	836 (13)	82 (5)	20 (5)	62 (5)		
PR					<.0001	0.39
positive	3,426 (55)	1,043 (67)	263 (68)	780 (66)		
negative	1,797 (29)	420 (27)	97 (25)	323 (27)		
unknown	1,044 (17)	104 (7)	28 (7)	76 (6)		
HER2					0.66	0.85
negative	3,618 (58)	1,132 (72)	283 (73)	849 (72)		
positive	455 (7)	136 (9)	35 (9)	101 (9)		
unknown	2,194 (35)	299 (19)	70 (18)	229 (19)		
Clinical subtype					0.17	0.65
luminal A	2,384 (38)	694 (44)	168 (43)	526 (45)		
luminal B	686 (11)	241 (15)	59 (15)	182 (15)		
non luminal (HER2 positive)	155 (2)	43 (3)	14 (4)	29 (2)		
triple negative	402 (6)	124 (8)	29 (7)	95 (8)		
unknown	2,640 (42)	465 (30)	118 (30)	347 (29)		

Data are n (%) unless otherwise indicated. ER, oestrogen-receptor; PR, progestogen-receptor; HER2, human epidermal growth factor receptor 2.

Association between T2D/insulin treatment and breast cancer characteristics

After adjustment for age, year of index date, SES, CDS and the use of glucocorticoids, oestrogen-progestogen contraceptives, and HRT, women with T2D were more often diagnosed with a larger tumour (OR (95% CI) = 1.22 [1.08-1.38]), a more advanced lymph node status (1.31 [1.12-1.53]), a more advanced tumour stage (1.28 [1.13-1.44]) and a higher grade (1.22 [1.08-1.39]), but less often with a PR-negative breast cancer (0.77 [0.67-0.89]) than women without T2D. No statistically significant associations were found for the other breast cancer characteristics (Fig. 1 and Supplementary Table 2).

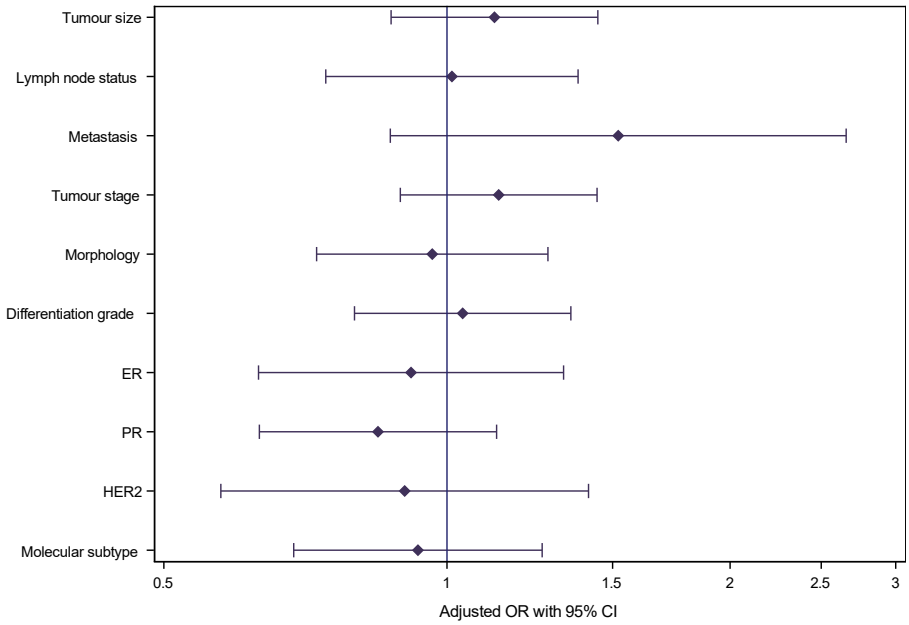


Model was adjusted for age, year of index date, SES, CDS, and use of glucocorticoids, oestrogen-progestogen contraceptives and HRT in the year prior to index date.

Abbreviations: ER, oestrogen-receptor; PR, progestogen-receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; 95% CI, 95% confidence interval.

Figure 1 Effect of T2D (N = 1,567) vs. no diabetes (N = 6,267) on developing breast cancer characteristics

INDEX



Model was adjusted for duration of T2D, age, year of index date, SES, CDS, and use of glucocorticoids, oestrogen-progestogen contraceptives and HRT in the year prior to index date.
Abbreviations: ER, oestrogen-receptor; PR, progestogen-receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; 95% CI, 95% confidence interval.

Figure 2 Effect of insulin (analogue) treatment (N = 388) vs. no insulin (analogue) treatment (N = 1,179) on developing breast cancer characteristics among women with T2D

Among women with breast cancer and T2D, no statistically significant associations were found between the use of insulin (analogues) and breast cancer characteristics (Fig. 2 and Supplementary Table 2).
Also, no statistically significant association was found between duration of insulin use and any of the breast cancer characteristics (Supplementary Fig. 2 and Supplementary Table 2). Women with T2D with an average daily insulin dose ≥40.9 IU tended to have smaller tumours (OR [95% CI]: 0.63 [0.41-0.95]) and less advanced tumours (0.64 [0.43-0.95]) than women with T2D with an average daily insulin dose <40.9 IU. No statistically significant association was found for the other breast cancer characteristics (Supplementary Fig. 3 and Supplementary Table 2).

Subgroup analyses

After adjustment for age and use of statins in the year prior to index date, use of insulin analogues (N = 236) was not associated with any of the breast cancer characteristics compared to human insulin (N = 59) (Supplementary Table 2).

Conclusions

The results of this retrospective nested case-control study show that T2D was associated with more advanced stages of breast cancer. Women with T2D were at increased risk to be diagnosed with a larger tumour, a more advanced lymph node status, a more advanced tumour stage, and a higher grade but at decreased risk to be diagnosed with a PR-negative tumour than women without diabetes. Among women with T2D, no differences in any pathologic breast cancer characteristic were found between the insulin (analogues) users and the noninsulin (analogues) users.

The literature regarding the association between diabetes and pathologic breast cancer characteristics is scarce,[6, 22-27] but the majority is consistent with our findings. These studies also concluded that patients with T2D presented with larger tumours[23, 24, 26, 27], higher rates of lymph node metastasis,[22-24] more advanced stages,[22, 27] and higher-grade tumours[25]. Furthermore, these studies[6, 22-27] also determined the association between diabetes and hormone receptor status (ER, PR and HER2). Only one study reported a statistically significant association between diabetes and ER.27 Three studies[23, 24, 27] found that breast cancer among women with diabetes was more often PR negative, which was not found in the current study. Similar to our results, none of the studies reported a statistically significant association between diabetes and HER2. Only Bronsveld et al.[6] and He et al.[22] also reported on molecular subtype. Neither found compelling evidence that women with diabetes develop different breast cancer subtypes than women without diabetes.

Although many of our findings were confirmed in other studies, it should be kept in mind that the studied populations probably differed in terms of race/ethnicity and age. Because disparities in breast cancer characteristics by race and ethnicity are well established,[28] results may not be completely generalizable.

Even fewer studies investigated whether the use of insulin (analogues) was associated with breast cancer characteristics.[6, 25, 29] In a retrospective cohort study,[29] insulin usage was found to be associated with a higher rate of angiolymphatic invasion, although this was based on nine insulin users only. Bronsveld et al.[6] did not observe evidence for strong associations with clinicopathological subtypes. One study compared the characteristics of insulin (n = 219) and noninsulin (n = 243) users and did not find statistically significant differences regarding clinicopathological breast cancer characteristics.[25]

To our best knowledge, no studies with a nested case-control design looked at the effect of insulin (analogue) use on clinicopathological breast cancer characteristics. In our study, no association regarding duration, dose, or type of insulin treatment with regard to breast cancer characteristics was found. However, it might be possible that we had insufficient power to detect a statistically significant association because the overall number of insulin (analogue) users was small. Furthermore, the used regression model assumes that some property of the outcome is linearly related to the exposure. If larger numbers are available, it will be worthwhile to explore the justification of this assumption or that using cubic spline functions would be more appropriate.[30]

INDEX

Although T2D was associated with more advanced stages of breast cancer, this association is not per definition causal. It is known that there are regional differences in the participation rate for routine screening for breast cancer in the Netherlands. In the large cities in the Randstad, the participation rate is the lowest. However, no differences were observed between women with T2D and women without diabetes regarding the distribution of the large cities in the Randstad versus other cities. Furthermore, it has been hypothesized that women with diabetes might have a lower participation rate because of the concurrent treatment of the chronic diseases associated with diabetes.[31] In the Netherlands, women aged 50-75 years are invited to attend a free breast cancer screening mammography regardless of comorbidity. Therefore, it is also likely that there is no difference regarding participation rates among women with and women without diabetes. Furthermore, breast cancers detected in mammography screening are associated with more favourable prognosis than breast cancers found outside of screening, because the distribution of molecular subtype of screen-detected breast cancers is different than the distribution of breast cancers found outside of screening.[32] In the current study, a subgroup analysis among women eligible for screening (50-75 years of age) showed the same results as the main analyses.

A possible suggested pathway for the association between T2D and breast cancer characteristics is hyperinsulinemia, related to underlying insulin resistance, that might stimulate tumour growth. Insulin may work directly on epithelial cells or indirectly by activating insulin-like growth factor pathways or altering endogenous sex hormones.[33-35] Insulin levels are already high in people with impaired glucose tolerance at the time of diagnosis of diabetes.[36] Moreover, Goodwin et al. showed that insulin levels were related to tumour stage, nodal stage, and tumour grade. Insulin levels were not related to nuclear grade, lymphatic invasion, ER, or PR.[37] In our study, exogenous insulin did not show an association with different breast cancer characteristics, which might be explained by the fact that insulin analogues may have an altered metabolic action and an altered mitogenic action than human insulin.[38]

INDEX

Some limitations should be kept in mind when interpreting the results of the present study. First, it was not possible to adjust for all important confounders. For instance, no information was available regarding mammography/screening, body mass index (BMI) or menopausal status. As obesity is a major risk factor for T2D, this could have influenced our results. However, Wolf et al.[27] showed that women with diabetes presented with a larger tumour size at diagnosis and a more advanced stage, even after adjustment for BMI. As the mean age in the current study was 71 years, our findings primarily apply to postmenopausal women. Whether a period of 4 years prior to breast cancer diagnosis is sufficient to determine cumulative insulin use is also debatable. For the current study, the decision entailed a trade-off between keeping sufficient numbers and a reasonable period to determine insulin use appropriately. Sensitivity analyses regarding the period prior to breast cancer diagnosis was outside the scope of the study. Furthermore, only women pharmaceutically treated for their T2D were included. Some misclassification of T2D might have occurred as weight loss can result in remission of T2D.[39] When interpreting the results regarding insulin versus no insulin,

it should be kept in mind that patients in both groups used NIBGLDs as well. The individual potential associations between NIBGLD and breast cancer characteristics might have influences our results. However, we believe that these influences were minimal because both groups had a similar distribution regarding NIBGLD use. The results in our study regarding breast cancer stages and duration, dose, and type of insulin use should be interpreted with caution, as the numbers were low, though with a long follow-up, and results were not even near statistically significant.
Overall, this is the first study using the linkage between the NCR and the Out-patient Pharmacy Database of the PHARMO Database Network for the association between T2D/insulin (analogue) use and different pathologic breast cancer characteristics. Through linking of these databases, a unique cohort was created taking advantage of the high-quality data on cancer and detailed information on medication use. This linkage resulted in one of the largest detailed cohorts of women with breast cancer and T2D/insulin (analogues) use. Because of the design of the study, misclassification was limited to a minimum.

Conclusion
Our study suggests that women with T2D present with more advanced breast tumours at diagnosis than women without T2D. Among women with T2D, the use of insulin (analogues) is not associated with developing more aggressive breast cancer tumours. Based on the current data we see no reason to restrain the use of insulin (analogues) among women with T2D with regard to its effects on breast cancer subtype and expected subsequent prognosis.

Acknowledgements

The authors would like to thank all the health care providers contributing information to the PHARMO Database Network.

Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
JO and RH are employees of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. MH, PV, AH, HB, MS and GN declare no conflict of interest.

References

1. World Health Organization (WHO). Global report on diabetes. Available from: http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf?ua=1. Accessed December 15, 2016.
2. Liao S, Li J, Wei W, Wang L, Zhang Y, Li J, et al. Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature. **Asian Pac J Cancer Prev**. 2011; 12: 1061-1065.
3. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. **CA Cancer J Clin**. 2015; 65: 87-108.
4. (CBS) CBvdS. Bevolking; kerncijfers. Available from: http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=37296NED&D1=0-2&D2=39-67&VW=T. Accessed August 31, 2018.
5. Integraal Kankercentrum Nederland (ikNL). Incidentie | Borst; Landelijk; Vrouw; Invasief. Available from: https://www.cijfersoverkanker.nl/selecties/incidentie_borst/img5b8902a6817e0. Accessed August 31, 2018.
6. Bronsveld HK, Jensen V, Vahl P, De Bruin ML, Cornelissen S, Sanders J, et al. Diabetes and Breast Cancer Subtypes. **PLoS One**. 2017; 12: e0170084.
7. La Vecchia C, Giordano SH, Hortobagyi GN, Chabner B. Overweight, obesity, diabetes, and risk of breast cancer: interlocking pieces of the puzzle. **Oncologist**. 2011; 16: 726-729.
8. Chang SC, Yang WV. Hyperglycemia, tumorigenesis, and chronic inflammation. **Crit Rev Oncol Hematol**. 2016; 108: 146-153.
9. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. **Diabetologia**. 2009; 52: 1766-1777.
10. Hemkens LG, Grouven U, Bender R, Gunster C, Gutschmidt S, Selke GW, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. **Diabetologia**. 2009; 52: 1732-1744.
11. Jonasson JM, Ljung R, Talback M, Haglund B, Gudbjornsdottir S, Steineck G. Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. **Diabetologia**. 2009; 52: 1745-1754.
12. Gallagher EJ, LeRoith D. The proliferating role of insulin and insulin-like growth factors in cancer. **Trends Endocrinol Metab**. 2010; 21: 610-618.
13. Grimberg A. Mechanisms by which IGF-I may promote cancer. **Cancer Biol Ther**. 2003; 2: 630-635.
14. Peairs KS, Barone BB, Snyder CF, Yeh HC, Stein KB, Derr RL, et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. **J Clin Oncol**. 2011; 29: 40-46.
15. Wu JW, Azoulay L, Majdan A, Boivin JF, Pollak M, Suissa S. Long-Term Use of Long-Acting Insulin Analogs and Breast Cancer Incidence in Women With Type 2 Diabetes. **J Clin Oncol**. 2017; 35: 3647-3653.

16. Bronsveld HK, ter Braak B, Karlstad O, Vestergaard P, Starup-Linde J, Bazelier MT, et al. Treatment with insulin (analogues) and breast cancer risk in diabetics; a systematic review and meta-analysis of in vitro, animal and human evidence. **Breast Cancer Res**. 2015; 17: 100.
17. But A, De Bruin ML, Bazelier MT, Hjellvik V, Andersen M, Auvinen A, et al. Cancer risk among insulin users: comparing analogues with human insulin in the CARING five-country cohort study. **Diabetologia**. 2017; 60: 1691-1703.
18. Integraal kankercentrum Nederland (ikNL). Netherlands Comprehensive Cancer Organisation. Available from: https://www.iknl.nl/over-iknl/about-iknl/what. Accessed September 24, 2018.
19. Putnam KG, Buist DS, Fishman P, Andrade SE, Boles M, Chase GA, et al. Chronic disease score as a predictor of hospitalization. **Epidemiology**. 2002; 13: 340-346.
20. Catalan VS, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. **Value Health**. 2000; 3: 417-426.
21. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thurlimann B, Senn HJ, et al. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. **Ann Oncol**. 2011; 22: 1736-1747.
22. He DE, Bai JW, Liu J, Du CW, Huang WH, Zhang GJ. Clinicopathological characteristics and prognosis of breast cancer patients with type 2 diabetes mellitus. **Mol Clin Oncol**. 2015; 3: 607-612.
23. Hou G, Zhang S, Zhang X, Wang P, Hao X, Zhang J. Clinical pathological characteristics and prognostic analysis of 1,013 breast cancer patients with diabetes. **Breast Cancer Res Treat**. 2013; 137: 807-816.
24. Liao S, Li J, Wang L, Zhang Y, Wang C, Hu M, et al. Type 2 diabetes mellitus and characteristics of breast cancer in China. **Asian Pac J Cancer Prev**. 2010; 11: 933-937.
25. Mu L, Zhu N, Zhang J, Xing F, Li D, Wang X. Type 2 diabetes, insulin treatment and prognosis of breast cancer. **Diabetes Metab Res Rev**. 2017; 33.
26. Schrauder MG, Fasching PA, Haberle L, Lux MP, Rauh C, Hein A, et al. Diabetes and prognosis in a breast cancer cohort. **J Cancer Res Clin Oncol**. 2011; 137: 975-983.
27. Wolf I, Sadetzki S, Gluck I, Oberman B, Ben-David M, Papa MZ, et al. Association between diabetes mellitus and adverse characteristics of breast cancer at presentation. **Eur J Cancer**. 2006; 42: 1077-1082.
28. Ooi SL, Martinez ME, Li CI. Disparities in breast cancer characteristics and outcomes by race/ethnicity. **Breast Cancer Res Treat**. 2011; 127: 729-738.
29. Goldvaser H, Rizel S, Hendler D, Neiman V, Shepshelovich D, Shochat T, et al. The Association between Treatment for Metabolic Disorders and Breast Cancer Characteristics. **Int J Endocrinol**. 2016; 2016: 4658469.
30. Harrell FE, Jr., Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. **J Natl Cancer Inst**. 1988; 80: 1198-1202.

31. Maruthur NM, Bolen S, Brancati FL, Clark JM. Obesity and mammography: a systematic review and meta-analysis. **J Gen Intern Med**. 2009; 24: 665-677.
32. Sihto H, Lundin J, Lehtimaki T, Sarlomo-Rikala M, Butzow R, Holli K, et al. Molecular subtypes of breast cancers detected in mammography screening and outside of screening. **Clin Cancer Res**. 2008; 14: 4103-4110.
33. Jiralerspong S, Palla SL, Giordano SH, Meric-Bernstam F, Liedtke C, Barnett CM, et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. **J Clin Oncol**. 2009; 27: 3297-3302.
34. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. **Nat Rev Cancer**. 2004; 4: 579-591.
35. Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B. Diabetes mellitus and breast cancer. **Lancet Oncol**. 2005; 6: 103-111.
36. Nijpels G, Popp-Snijders C, Kostense PJ, Bouter LM, Heine RJ. Fasting proinsulin and 2-h post-load glucose levels predict the conversion to NIDDM in subjects with impaired glucose tolerance: the Hoorn Study. **Diabetologia**. 1996; 39: 113-118.
37. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. **J Clin Oncol**. 2002; 20: 42-51.
38. Varewijck AJ, Janssen JA. Insulin and its analogues and their affinities for the IGF1 receptor. **Endocr Relat Cancer**. 2012; 19: F63-75.
39. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. **Lancet**. 2018; 391: 541-551.

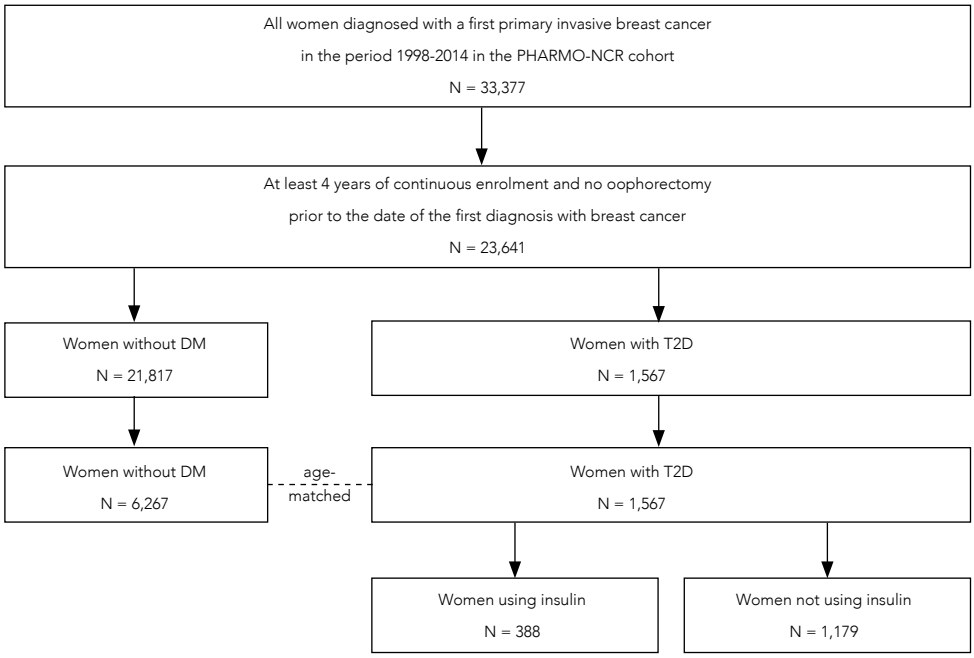
Supporting Information

Supplementary Table 1 Scoring rules CDS-3

Chronic disease	Medication class(es)	ATC code	Scoring rules	
Heart disease	1. Anti-coagulants, haemostatics	1. B01A	1 class	= 3
	2. Cardiac agents, non-dihydropyridine CCB, nitrates	2. C01, C08D, C09BB10	2 classes	= 5
	3. Diuretic loop	3. C03C	3 classes	= 7
Renal failure	Calcium acetate, Sorbisterit, Retacrit, Fosrenol, Zemplar	V03AE, A12AA12,B03XA, H05BX02	Score	= 6
Malignancy	Oncolytic agents, colony stimulating factor, anti-hormones	L01A, L01C, L02B, L01BB, L01BC, L03AA	Score	= 4
Parkinson's disease	L-Dopa, dopamine-agonists	N04BA, N04BC, N04BD	Score	= 3
Rheumatic disease	Methotrexate, cyclosporine, sulfasalazine, TNF-⍰ blocker	L04AA13, L04AD01, L04AX01, L04AX03, L04AB	Score	= 3
Ulcer/GERD	Proton pump inhibitors	A02BC	Score	= 3
Glaucoma	Beta-blockers, prostaglandins, carbonic anhydrase inhibitor	S01E	Score	= 3
Epilepsy	1. Anticonvulsants not lithium	1. N03		
	2. Lithium	2. N05AN	Class 1 & not 2	= 3
	1. Inhaled beta-adrenergic	1. R03AC, R03AK		
	2. Inhaled corticosteroid	2. R03BA, R03AK		
Respiratory illness	3. inhaled parasympathicolytics	3. R03BB	1 class	=1
	4. Leukotriene antagonist	4. R03DC	≥2 classes	=3
	5. Theophylline	5. R03DA		
Hypertension	1. ACEI, AT2R-blocker, renin inhibitor	1. C09A-C09D, C09X	Class 1	=2
	2. Beta-blockers, dihydropyridine CCB, non-loop diuretics	2. C03A, C03B, C03D, C03E, C07, C08C, C09B, C09D	Class 2 & not 1	= 1
Diabetes	Insulin / oral hypoglycaemic drugs	A10	Score	= 1
High cholesterol	Lipid lowering agents; statins, fibrates, ezetimibe	C10	Score	= 1
Rhinitis	Nasal corticoid	R01AD	Score	= 1
Psychosis	Antipsychotics	N05A	Score	= 1
Parkinson's disease	L-Dopa, dopamine-agonists	N04BA, N04BC, N04BD	Score	= 3

ATC = anatomical therapeutic chemical; ACE = angiotensin-converting enzyme; AT2R = angiotensin II-receptor; CCB = calcium-channel blocker; TNF = tumour necrosis factor; GERD = gastro-oesophageal reflux disease

INDEX



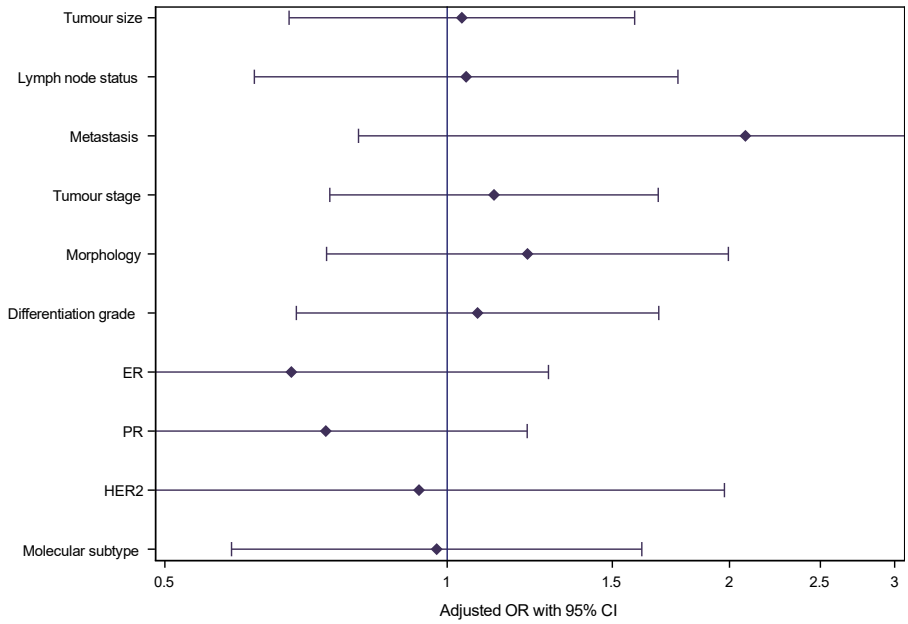
Supplementary Figure 1 Flow chart of patient selection

INDEX

Supplementary Table 2 Effect of exposure vs. no exposure on developing breast cancer characteristics

	T2DM vs no DM	
	Crude OR (95% CI)	Adjusted OR (95% CI)
Tumour size	1.21 (1.09-1.35)	1.22 (1.08-1.38)
Lymph node status	1.23 (1.07-1.42)	1.31 (1.12-1.53)
Metastasis	1.28 (0.98-1.67)	1.31 (0.98-1.75)
Tumour stage	1.24 (1.12-1.38)	1.28 (1.13-1.44)
Morphology	0.86 (0.76-0.97)	0.94 (0.82-1.07)
Grade	1.18 (1.05-1.33)	1.22 (1.08-1.39)
ER	1.01 (0.85-1.19)	1.04 (0.86-1.25)
PR	0.77 (0.68-0.87)	0.77 (0.67-0.89)
HER2	0.96 (0.78-1.17)	0.93 (0.75-1.16)
Clinical subtype	1.10 (0.96-1.26)	1.10 (0.94-1.27)
	Insulin (analogues) vs. no insulin (analogues)	
	Crude OR (95% CI)	Adjusted OR (95% CI)
Tumour size	1.08 (0.86-1.36)	1.12 (0.87-1.45)
Lymph node status	1.07 (0.81-1.41)	1.01 (0.74-1.38)
Metastasis	1.40 (0.85-2.30)	1.52 (0.87-2.66)
Tumour stage	1.11 (0.89-1.39)	1.13 (0.89-1.44)
Morphology	0.93 (0.72-1.20)	0.96 (0.73-1.28)
Grade	1.11 (0.87-1.42)	1.04 (0.80-1.35)
ER	1.01 (0.72-1.41)	0.92 (0.63-1.33)
PR	0.89 (0.68-1.16)	0.84 (0.63-1.13)
HER2	1.04 (0.69-1.56)	0.90 (0.57-1.41)
Clinical subtype	1.04 (0.79-1.37)	0.93 (0.69-1.26)
	Short vs. long use of insulin (analogues)	
	Crude OR (95% CI)	Adjusted OR (95% CI)
Tumour size	1.09 (0.73-1.62)	1.04 (0.68-1.58)
Lymph node status	0.92 (0.57-1.50)	1.05 (0.62-1.76)
Metastasis	1.43 (0.62-3.31)	2.08 (0.80-5.38)
Tumour stage	1.07 (0.73-1.56)	1.12 (0.75-1.68)
Morphology	1.24 (0.79-1.95)	1.22 (0.74-1.99)
Grade	1.16 (0.76-1.77)	1.08 (0.69-1.68)
ER	0.71 (0.39-1.28)	0.68 (0.36-1.28)
PR	0.82 (0.51-1.31)	0.74 (0.45-1.22)
HER2	0.91 (0.45-1.84)	0.93 (0.44-1.98)
Clinical subtype	1.02 (0.63-1.64)	0.97 (0.59-1.61)
	Low vs. high dose of insulin (analogues)	
	Crude OR (95% CI)	Adjusted OR (95% CI)
Tumour size	0.62 (0.42-0.93)	0.63 (0.41-0.95)
Lymph node status	0.87 (0.54-1.42)	0.75 (0.45-1.26)
Metastasis	0.70 (0.30-1.61)	0.72 (0.30-1.74)
Tumour stage	0.67 (0.46-0.98)	0.64 (0.43-0.95)
Morphology	0.75 (0.48-1.18)	0.80 (0.50-1.30)
Grade	0.78 (0.51-1.18)	0.70 (0.45-1.08)
ER	0.89 (0.49-1.60)	0.73 (0.39-1.37)
PR	1.08 (0.68-1.72)	0.95 (0.59-1.55)
HER2	0.76 (0.37-1.53)	0.64 (0.30-1.36)
Clinical subtype	0.78 (0.48-1.26)	0.67 (0.41-1.11)
	Insulin analogues vs. human insulin	
	Crude OR (95% CI)	Adjusted OR (95% CI)
Tumour size	0.81 (0.47-1.41)	0.98 (0.55-1.75)
Lymph node status	1.03 (0.57-1.87)	0.95 (0.51-1.78)
Metastasis	0.51 (0.15-1.69)	0.55 (0.16-1.95)
Tumour stage	0.74 (0.45-1.23)	0.77 (0.44-1.33)
Morphology	0.65 (0.36-1.19)	0.82 (0.44-1.55)
Grade	0.87 (0.47-1.61)	0.94 (0.49-1.80)
ER	0.72 (0.29-1.78)	0.58 (0.22-1.49)
PR	0.88 (0.43-1.83)	0.78 (0.37-1.65)
HER2	4.45 (0.58-34.02)	3.49 (0.45-27.31)
Clinical subtype	1.05 (0.40-2.74)	1.05 (0.42-2.64)

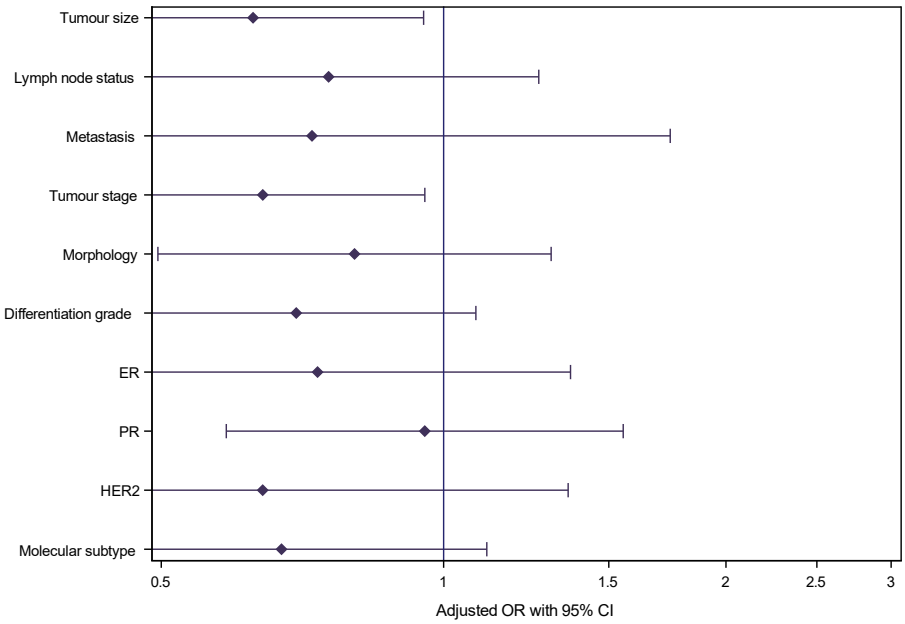
OR = odds ratio; CI = confidence interval; ER = oestrogen-receptor; PR = progestogen-receptor; HER2 = human epidermal growth factor receptor 2.



Model was adjusted for duration of T2D, age, CDS and use of HRT in the year prior to index date. Abbreviations: ER, oestrogen-receptor; PR, progestogen-receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; 95% CI, 95% confidence interval; T2D = type 2 diabetes; CDS = chronic disease score.

Supplementary Figure 2 Effect of long insulin use (N = 194) versus short insulin use (N = 194) on developing breast cancer characteristics among women with T2D using insulin

INDEX



Model was adjusted for duration of T2D, age, CDS and year of index date. Abbreviations: ER, oestrogen-receptor; PR, progestogen-receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; 95% CI, 95% confidence interval; T2D = type 2 diabetes; CDS = chronic disease score.

Supplementary Figure 3 Effect of high insulin dose (N = 194) versus low insulin dose (N = 194) on developing breast cancer characteristics among women with T2D using insulin

CHAPTER 8

Sex- and site-specific differences in colorectal cancer risk among people with type 2 diabetes

Jetty A. Overbeek, Josephina G. Kuiper, Amber A.W.A. van der Heijden, Mariette Labots, Ulrike Haug, Ron M.C. Herings, Giel Nijpels

Int J Colorectal Dis. 2018 Nov 12. doi: 10.1007/s00384-018-3191-7

Abstract

Purpose: The prevalence of colorectal cancer (CRC) is higher among patients with type 2 diabetes mellitus (T2D) than among patients without diabetes. Furthermore, men are at higher risk for developing CRC than women in the general population and also subsite-specific risks differ per sex. The aim was to evaluate the impact of T2D on these associations.

Methods: A population-based matched cohort study was performed using data from the PHARMO Database Network. Patients with T2D were selected and matched (1:4) to diabetes free controls. Cox proportional hazards models were used to estimate hazard ratios (HRs) for CRC and its subsites. HRs were determined per sex and adjusted for age and socioeconomic status. The ratio of distal versus proximal colon cancer was calculated for people with T2D and controls per sex and stratified by age.

Results: Over 55,000 people with T2D were matched to >215,000 diabetes free controls. Men and women with T2D were 1.3 times more likely to develop CRC compared to controls. Men with T2D were at higher risk to develop distal colon cancer (HR (95% confidence interval (CI)), 1.42 (1.08-1.88)), and women with T2D were at higher risk for developing proximal colon cancer (HR (95% CI), 1.58 (1.13-2.19)). For rectal cancer, no statistically significant risk was observed for both men and women.

Conclusions: Sex-specific screening strategies and prevention protocols should be considered for people with T2D. More tailored screening strategies may optimize the effectiveness of CRC screening in terms of reducing incidence and mortality.

INDEX

Introduction

Type 2 diabetes mellitus (T2D) and colorectal cancer (CRC) are increasing health problems. Currently, CRC is the third most common cancer worldwide and the second most common cancer in Europe.[1] The number of people with CRC is expected to increase due to demographic changes, obesity, and lack of physical activity. Also the prevalence of T2D is increasing worldwide.[2,3] In the Netherlands, the prevalence of T2D more than doubled between 1999 and 2014, mainly due to demographic changes, but probably also due to overweight and screening initiatives.[4]

Regardless of T2D, CRC incidence, prevalence, and mortality are higher among men than women.[5,6] However, women aged ≥55 years are more often diagnosed with proximal (right-sided) CRC,[7] which is associated with more aggressive form of neoplasia than distal (left-sided) CRC.[8] Among these reasons, sex-specific screening strategies have been proposed.[9]

Several observational studies have demonstrated an increased risk of CRC in people with T2D.[10,11] Several mechanisms have been proposed to explain the higher prevalence of CRC in people with hyperglycaemia, such as hyperglycaemia in itself, hyperinsulinemia, which leads to increased insulin-like growth factor (IGF) levels, and insulin resistance.[12]

Some reviews and meta-analyses regarding the association between T2D and CRC reported a higher risk of CRC among women with T2D (compared to their disease free controls)[13] than among men with T2D (compared to their disease free controls),[14] while others concluded that the risk among people with T2D compared to people without T2D is regardless of sex.[15-18]

Sex-specific differences in risk of anatomical subsites of CRC in people with T2D are less studied. As people with T2D already undergo health check-ups regularly, it is important to know whether sex-specific screening strategies would also be necessary for people with T2D. Therefore, the aim of the current study was to evaluate the sex-specific risk of subsites of CRC in people with T2D compared to people without diabetes in a population-based cohort. In this study, the unique linkage between the General Practitioner (GP) Database of the PHARMO Database Network and the Netherlands Cancer Registry (NCR) was used, creating a comprehensive large database with detailed and high-quality data on cancer and T2D.

Materials and Methods

INDEX

Data sources

Data for this cohort study were obtained from the GP Database of the PHARMO Database Network[19] and the NCR. The GP Database comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists, and healthcare product/drug prescriptions. Currently, the GP Database covers a catchment area of approximately 3.5 million inhabitants. Recently, the GP Database was linked to the NCR on a patient-level. The NCR is maintained by the Netherlands Comprehensive Cancer Organisation (IKNL)[20] and contains information on newly

diagnosed patients with cancer, coded according to the WHO International Classification of Diseases for Oncology (ICD-O-3). The NCR is notified, on a daily basis, for new patients with cancer by pathology departments, general hospitals, and radiotherapy institutes. The construct of the record linkage method is described elsewhere.[21] The privacy committees of the NCR and the PHARMO Institute approved this study.

Study population

From PHARMO's GP Database, all people diagnosed with T2D between 2006 and 2014 were selected. T2D was defined as a recorded episode for T2D or ≥2 prescriptions of a blood glucose lowering drug, excluding insulin within a 6-month period at any time in the available medication records. The date of the first recorded episode for T2D, the second prescription, or the first examination regarding diabetes, whichever occurred first, was defined as the index date. People with another type of diabetes, using insulin prior to index date, <40 years of age at index date, or having a history of cancer were excluded (see Supplementary Table S1 for codes used for exclusion criteria). Patients with <12 months of continuous enrolment prior to index date were excluded as well, in order to ensure newly diagnosed people with T2D.
People with T2D were randomly matched (1 up to 4) to controls on sex, year of birth (± 2 years), GP practice, and start year of enrolment in the database. Matched controls received the same index date as their matched cases. Controls who had a history of diabetes, were <40 years of age at index date, had <12 months of continuous enrolment prior to index date, or had a history of cancer were excluded. Furthermore, controls had to be alive and known in the GP Database at index date and could not be matched to themselves or more than once. All people with T2D and matched controls were followed from index date until diagnosis of CRC, diagnosis of (another type of) diabetes, end of database registration (i.e., patient moves out of the catchment area), death, or end of study period (December 31, 2014), whichever occurred first.

Characteristics

For all included people, the following was determined at index date: age, socioeconomic status (SES), available history and follow-up in the database, and year of index date. Furthermore, the use of aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), statins, antihypertensives, and hormone replacement therapy (HRT) was determined in the year prior to index date (see Supplementary Table S1 for ATC codes). SES was derived from Statistics Netherlands,[22] which based SES on salary per 6-digit zip code determined in December 2008.

INDEX

Outcome

During follow-up, the occurrence of the initial diagnosis of primary, localized (or non-metastatic) CRC was obtained from the NCR and used as outcome in the analyses. Proximal colon cancers included malignant neoplasms of cecum, appendix, ascending colon, hepatic flexure, and transverse colon. Distal colon cancers included malignant neoplasms of splenic

flexure, descending colon, and sigmoid colon. Rectal cancer included malignant neoplasm of rectum. Malignant neoplasm of overlapping sites of colon, unspecified sites of colon, and rectosigmoid junction were included when analysing overall CRC.

Statistical methods

Characteristics of all included people were reported descriptively. Differences in characteristics between men and women with T2D were compared with men and women without diabetes and assessed using chi-square tests for categorical variables and ANOVA tests for continuous variables.

Unadjusted incidence rates (IRs) for CRC were determined by dividing the total number of events by the total number of patient years at risk (summed number of years of follow-up). To generate hazard ratios (HR) and their corresponding 95% confidence intervals (CI), Cox proportional hazards model, adjusted for age, SES, and drugs known to (potentially) influence risk of CRC (aspirin, non-aspirin NSAIDs, statins, antihypertensives, and HRT) were used. The analyses were stratified according to three categories regarding anatomic subsites (proximal colon, distal colon, and rectum) and risk estimates were also calculated for each subsite separately.

As several studies have reported a shift of CRC localization by age,[7] it was determined whether the same trend was observed among people with T2D. The number of distal (including rectal) colon cancers was divided by the number of proximal colon cancers to calculate the ratio of distal versus proximal colon cancer. This ratio was calculated for people with T2D and no diabetes per sex and was stratified by age (50-69 and ≥70 years) at index date.

All data were analysed using SAS programs organized within SAS Enterprise Guide version 4.3 (SAS Institute Inc., Cary, NC, USA) and conducted under Windows using SAS version 9.2.

Sensitivity analyses

Reported associations in observational studies can be affected by detection (protopathic) bias, i.e., an increased odds of detecting cancer shortly after the onset of diabetes.[10] In order to explore the extent of detection bias, the risk of (anatomic subsites of) CRC was stratified by follow-up period (0-91 days, >91-182 days, >182-365 days and >365 days). Per follow-up period, people with the date of CRC not within the follow-up period were censored. Only follow-up up to the end of that specific follow-up period, end of follow-up, or date of CRC, whichever occurred first, was used to calculate the total number of patient years at risk.

INDEX

Results

Patient characteristics

After applying all in- and exclusion criteria, 29,696 men and 25,349 women with T2D were included and matched to 116,570 and 99,437 diabetes free controls, respectively (see

Supplementary Fig. S1). Mean age at baseline was 62.1 years among men and 64.9 years among women. Baseline characteristics, such as age, SES, history in the database, and year of index date, were similar between people with T2D and people without diabetes. Available follow-up in the database was longer among cases compared to controls. Furthermore, people with T2D more often used aspirin, non-aspirin NSAIDs, statins and antihypertensives compared to the matched people without diabetes (see Table 1).

Table 1 General characteristics of people with T2D and no diabetes

	Men			Women		
	T2D N = 29,696 n (%)	no diabetes N = 116,570 n (%)	p-value	T2D N = 25,349 n (%)	no diabetes N = 99,437 n (%)	p-value
Age (years), mean ± SD	62.1 ± 10.9	62.0 ± 10.9	0.06	64.9 ± 12.2	64.8 ± 12.2	0.10
SES			0.99			0.99
low	7,460 (25)	29,247 (25)		6,570 (26)	25,722 (26)	
normal	9,481 (32)	37,217 (32)		8,281 (33)	32,507 (33)	
high	12,755 (43)	50,106 (43)		10,498 (41)	41,208 (41)	
History in database (years)			0.24			0.28
mean ± SD	4.0 ± 2.1	4.1 ± 2.1		3.9 ± 2.1	4.0 ± 2.1	
median (IQR)	3.8 (2.2-5.6)	3.8 (2.2-5.7)		3.6 (2.2-5.4)	3.6 (2.2-5.5)	
Follow-up in database (years)			<.0001			<.0001
mean ± SD	3.7 ± 2.2	3.5 ± 2.2		3.8 ± 2.2	3.7 ± 2.2	
median (IQR)	3.7 (1.9-5.5)	3.4 (1.7-5.3)		3.8 (2.0-5.6)	3.7 (1.8-5.5)	
Year of index date			0.60			0.53
2007-2008	6,205 (21)	24,691 (21)		5,644 (22)	22,477 (23)	
2009-2010	8,528 (29)	33,612 (29)		7,579 (30)	29,869 (30)	
2011-2012	8,059 (27)	31,447 (27)		6,598 (26)	25,688 (26)	
2013-2014	6,904 (23)	26,820 (23)		5,528 (22)	21,403 (22)	
Co-medication*						
aspirin	4,972 (17)	12,303 (11)	<.0001	3,236 (13)	8,197 (8)	<.0001
non-aspirin NSAIDs	6,999 (24)	22,274 (19)	<.0001	6,594 (26)	22,092 (22)	<.0001
statins	11,626 (39)	22,828 (20)	<.0001	8,800 (35)	15,712 (16)	<.0001
anthypertensives	13,208 (44)	28,925 (25)	<.0001	13,469 (53)	30,609 (31)	<.0001
HRT	-	-		814 (3)	3,656 (4)	<.01

SD, standard deviation; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; HRT, hormone replacement therapy, *Determined in the year prior to index date.

INDEX

Colorectal cancer

Figure 1 and Table 2 present the subsite-specific rates of CRC among men and women with T2D and their matched controls. Supplementary Table S2 presents the number of CRC events and person years at risk among men and women with T2D and no diabetes.

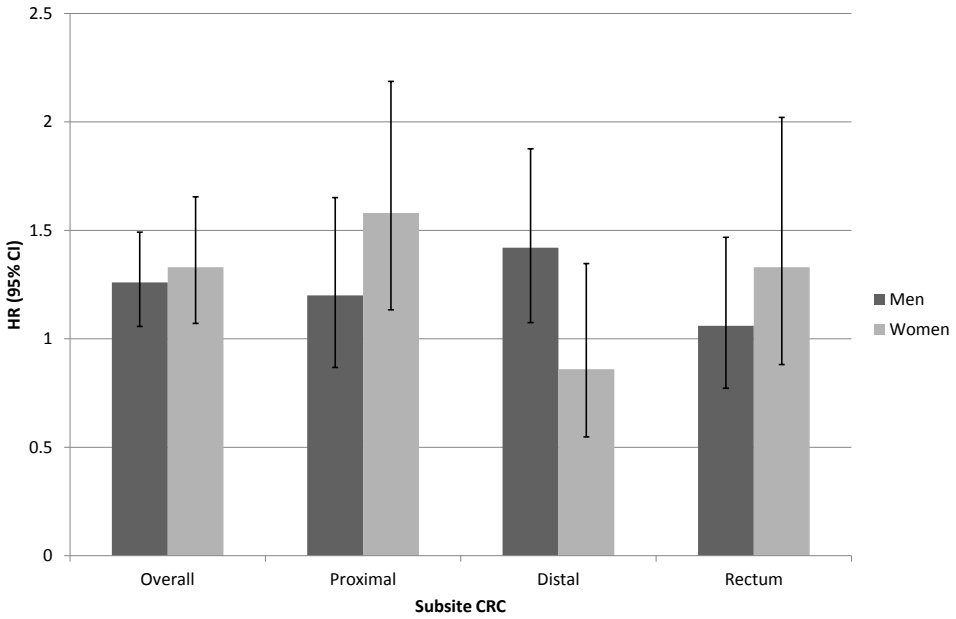


Figure 1 Difference between men and women in subsite CRC among people with T2DM compared to people without diabetes

Overall, both men and women with T2D were 1.3 times more likely to develop CRC compared to their controls without diabetes (Figure 1). However, differences regarding subsite-specific risks were observed between the sexes. Compared to diabetes free controls, men with T2D were at higher risk to develop distal colon cancer (HR (95% CI): 1.42 (1.08-1.88)) than women with T2D (HR (95% CI): 0.86 (0.55-1.35)). The same trend was observed in the anatomical subsites of distal colon cancer, except for cancer of the splenic flexure. Again compared to controls without diabetes, women with T2D were at higher risk to develop proximal colon cancer (HR (95% CI): 1.58 (1.13-2.19)) than men with T2D (HR (95% CI): 1.20 (0.87-1.65)). This difference was also observed for all subsites of proximal colon cancer, although not always statistically significant. Women with T2D had a higher risk to develop rectal cancer than men with T2D compared to diabetes free controls, but the risk in both men and women was not statistically significant (HR (95% CI) for men is 1.06 (0.77-1.47) and 1.33 (0.88-2.02) for women)

INDEX

Table 2 Incidence rates and hazard ratios of subsites of CRC among men and women with T2D and no diabetes

	Men				Women			
	T2D	no diabetes	T2D vs no diabetes		T2D	no diabetes	T2D vs no diabetes	
	n (%)	n (%)	HR*	(95% CI)	IR (95% CI)	IR (95% CI)	HR*	(95% CI)
colon and rectum	1.66 (1.43-1.92)	1.31 (1.20-1.43)	1.26	(1.06-1.49)	1.21 (1.00-1.45)	0.95 (0.85-1.05)	1.33	(1.07-1.65)
proximal	0.47 (0.35-0.61)	0.39 (0.33-0.45)	1.20	(0.87-1.65)	0.55 (0.41-0.72)	0.37 (0.31-0.44)	1.58	(1.13-2.19)
cecum	0.17 (0.10-0.27)	0.17 (0.13-0.22)	0.96	(0.57-1.62)	0.23 (0.14-0.34)	0.17 (0.13-0.22)	1.37	(0.83-2.27)
appendix	-	-	-	-	-	-	-	-
ascending colon	0.21 (0.13-0.31)	0.10 (0.08-0.14)	2.12	(1.26-3.59)	0.18 (0.10-0.28)	0.10 (0.07-0.13)	1.98	(1.09-3.61)
hepatic flexure	0.05 (0.02-0.12)	0.03 (0.01-0.05)	2.31	(0.83-6.48)	0.08 (0.04-0.16)	0.04 (0.02-0.07)	2.21	(0.92-5.32)
transverse colon	0.04 (0.01-0.09)	0.08 (0.05-0.11)	0.41	(0.14-1.18)	0.06 (0.02-0.14)	0.05 (0.03-0.08)	1.22	(0.47-3.13)
distal	0.66 (0.52-0.83)	0.46 (0.40-0.54)	1.42	(1.08-1.88)	0.26 (0.17-0.38)	0.29 (0.24-0.35)	0.86	(0.55-1.35)
splenic flexure	0.01 (0.00-0.05)	0.02 (0.01-0.04)	0.30	(0.04-2.37)	0.06 (0.02-0.14)	0.03 (0.01-0.05)	2.39	(0.82-6.93)
descending colon	0.07 (0.03-0.14)	0.03 (0.01-0.05)	2.56	(1.00-6.53)	0.02 (0.00-0.07)	0.03 (0.01-0.05)	0.60	(0.13-2.85)
sigmoid colon	0.58 (0.44-0.74)	0.41 (0.35-0.48)	1.42	(1.05-1.91)	0.18 (0.10-0.28)	0.23 (0.19-0.29)	0.72	(0.42-1.24)
rectum	0.46 (0.34-0.60)	0.42 (0.36-0.49)	1.06	(0.77-1.47)	0.33 (0.23-0.47)	0.26 (0.21-0.32)	1.33	(0.88-2.02)

*Adjusted for age, SES and the use of aspirin, non-aspirin NSAIDs, statins, antihypertensives, and HRT in the year prior to index date.

Figure 2 presents the ratio of distal (including rectal) versus proximal colon cancer stratified by T2D status in men (Fig. 2a) and women (Fig. 2b). As presented in Fig. 2a, distal colon cancer is more frequent than proximal colon cancer (i.e., ratio > 1) in men with T2D and no diabetes. The same is observed in men aged ≥70 years; however the ratio is lower than for men aged 50-69 years. As shown in Fig. 2b the ratio among women is also above 1 (i.e., more distal than proximal colon cancers), except for women with T2D aged ≥70 years, i.e., these women are more likely to be diagnosed with proximal colon cancer than with distal colon cancer. Generally, the ratio was lower for women than for men, i.e., irrespective of age and T2D status.

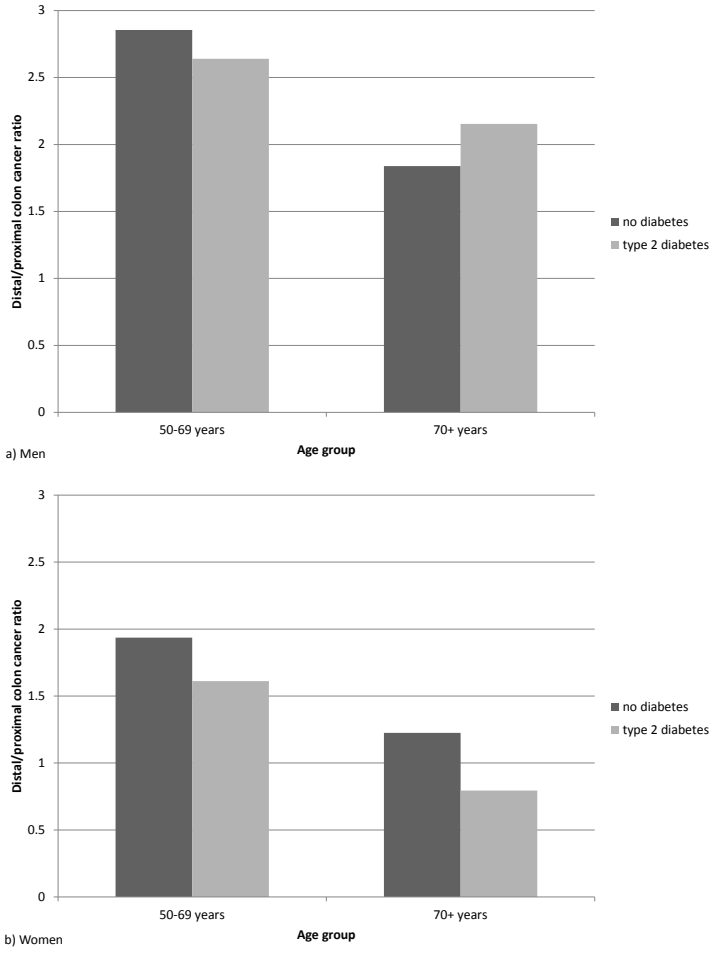


Figure 2 Ratio of distal (including rectal)/proximal colon cancer for people with T2D and no diabetes by age group among men (a) and women (b)

INDEX

Sensitivity analyses
To account for potential detection bias, risk of (anatomical subsites of) CRC was stratified by follow-up period (Supplementary Fig, S2). When considering a 1-year lag period, the risk of overall CRC and its subsites was similar than the risk calculated without a lag period; only the risk of distal colon cancer became slightly lower through consideration of a 1-year lag period. The differences in risk between men and women remained after applying the lag period.

Discussion and conclusion

In this population-based cohort study among more than 270.000 people, we observed a similarly increased risk of CRC among men and women with T2D compared to diabetes free controls. However, differences regarding the location of the CRC were observed. Compared to diabetes free controls, men with T2D had a higher increased risk of distal colon cancer than women with T2D, and women with T2D had a higher increased risk of proximal colon cancer than men with T2D. These findings remained after applying a 1-year lag period to account for detection bias. Furthermore, women with T2D aged ≥70 years are more likely to develop proximal rather than distal colon cancer.
The overall risk of CRC observed in our study among men and women with T2D compared to men and women without diabetes is in line with previously published papers.[13,15-17] Several epidemiological studies presented separate risks for proximal and distal colon cancer by sex among people with T2D,[11,23-27] but also regardless of diabetes.[9,28]
The majority of these studies among people with T2D showed a higher increased risk of proximal colon cancer in women with T2D (HR ranging from 1.6 to 1.8) than men with T2D (HR ranging from 1.4 to 1.6) compared to diabetes free controls, which is consistent with our finding.[11,23-25,27] One study[26] found, compared to diabetes free controls, a higher increased risk of overall, proximal, and distal CRC among men than women. However, men were almost twice more likely to be classified as current or former cigarette smoker and they believe effect modification from cigarette smoking status appeared to have contributed to the difference in risk observed by sex.
Our finding that, compared to diabetes free controls, men are at higher risk to develop distal colon cancer than women appears to be consistent with existing literature.[11,23-27] Four of these studies[23,25-27] found higher risks of distal colon cancer among men (HR ranging from 1.3 to 2.1) than women (HR ranging from 0.7 to 2.0). The other two studies[11,24] found a higher risk of distal colon cancer among women than among men, but the results of these studies were not statistically significant.
For rectal cancer, studies regarding its sex-specific association with T2D are less consistent. One meta-analysis[29] found a statistically significant association between diabetes and rectal cancer for men (HR (95% CI): 1.22 (1.07-1.40)), but not for women (1.09 (0.99-1.19)). Two studies[25,27] found a statistically significant increased risk of rectal cancer for women,

which was higher than the non-statistically significant increased risk for men. Other cohort studies[10,11,23] did not find a statistically significant association for men or women, which was similar to our study.

In the general population, differences in the association between sex and anatomic subsites of CRC have been explained by the fact that the proximal colon, distal colon and rectum have different embryological origins.[30,31] In addition, hormonal factors, (epi)genetic differences, dietary factors, and structural factors have been proposed.[9] Furthermore, tumour suppressor genes, point mutations, genetic instability, and responses of cells to growth stimulating hormones, such as IGF, may differ by CRC subsite.[11] As it is hypothesized that both diabetes and CRC involve over-expression of both the insulin and IGF receptors,[32] this potentially even more complicates the association. Epidemiological evidence also links hyperinsulinemia to changes in sex steroids.[33] Sex differences in relation to certain risk factors may modify risk for tumour development, such as alcohol consumption, smoking and red meat consumption.[31,34] All taken together, it is likely that all these factors interact and act differently at various locations of the colorectum.

The results from our study suggest that sex-specific screening strategies are even more important among people with diabetes. While women without diabetes are known to present with proximal colon cancer more often than men, we found that women with T2D have an even higher increased risk of proximal colon cancer than women without diabetes. Furthermore, women with T2D aged ≥70 years were even more likely to be diagnosed with a proximal colon cancer than with a distal colon cancer. More attention should be paid to the adherence to colonoscopy screening in this risk group, being better suited to detect lesions in the proximal colon than other screening options.

Some limitations of this observational study should be mentioned. First, possible important confounders, such as obesity, smoking status, physical inactivity and nutritional intake could not be corrected for in our analyses. However, previous epidemiological studies, presenting both crude and adjusted risks, showed that adjusting for these factors only slightly attenuated the risk. Second, only patients with a GP recorded diagnosis or treated with blood glucose lowering drugs were included. Therefore, misclassification of T2D could have occurred as some patients are undiagnosed.[35] Furthermore, detection bias is a common phenomenon. People with T2D are more likely to be diagnosed with cancer shortly after the onset of diabetes as compared to people without diabetes. By applying a one-year lag period we aimed to exclude this bias, although the right lag period to exclude detection bias remains unknown.[10] Finally, as only outcome information regarding CRC was available, other forms of cancer as competing outcomes could not be taken into account. However, this will not affect the differences observed between people with T2D compared to people without diabetes.

Overall, this is the first study using the linkage between the NCR and the GP Database of the PHARMO Database Network for the association between T2D and sex- and site-specific difference in CRC risk. By linking these databases, a unique cohort was created taking advantage of the high-quality data on cancer and detailed information regarding T2D. This linkage resulted, to our knowledge, to one of the largest, detailed cohorts of

INDEX

people with T2D in which the incidence of subsite-specific CRC could be studied. An advantage of using the GP Database for selecting people with T2D is including people with T2D not yet pharmacologically treated (i.e., also people treated with lifestyle interventions). The improved linkage gave us the opportunity to also analyse the association between T2D and anatomical subsites of CRC.
Furthermore, ascertainment of exposure was based on large and high-quality pharmaco-epidemiological databases, which is more reliable than self-reported questionnaires. Because of repeated information regarding exposure, patients' follow-up could be ended when (another type of) diabetes was diagnosed (i.e., decreasing the likelihood of misclassification of T2D).

Conclusion
Besides a similarly increased risk of CRC among men and women with T2D compared to diabetes free controls, we found a higher increased risk of proximal colon cancer among women with T2D than men with T2D and a higher increased risk of distal colon cancer among men with T2D than women with T2D, compared to diabetes free controls. Therefore, sex-specific screening and prevention protocols may be considered for people with T2D. More tailored screening strategies may optimize the effectiveness of CRC screening in terms of reducing CRC incidence and mortality and improving the quality of life. Furthermore, future studies investigating the association between T2D and CRC should include sex-specific and subsite-specific analyses.

Acknowledgements

The authors thank all the healthcare providers that contributed information to the PHARMO Database Network.

Conflict of interest

J.A.O., J.G.K. and R.M.C.H. are employees of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. A.A.W.A.H., M.L. and G.N. declare no conflicts of interest. U.H. is working at the Leibniz Institute for Prevention Research and Epidemiology - BIPS. Unrelated to this study, BIPS occasionally conducts studies financed by the pharmaceutical industry. Almost exclusively, these are post-authorization safety studies (PASS) requested by health authorities. The studies and the resulting publications are not influenced by the pharmaceutical industry.

INDEX

References

1. World Cancer Report 2014. Lyon: International Agency for Research on Cancer, 2014.
2. International Diabetes Federation. IDF DIABETES ATLAS, 2015.
3. World Health Organization. Global report on diabetes, 2016.
4. Overbeek JA, van der Heijden AW, Herings RM, et al. [Prevalence of diabetes mellitus in the Netherlands more than doubled in the period 1999-2014]. **Ned Tijdschr Geneeskd**. 2017;0:D673.
5. Rijksinstituut voor Volksgezondheid en Milieu. Dikkedarmkanker | Cijfers & Context | Huidige situatie | Volksgezondheidenzorg.info. https://www.volksgezondheidenzorg.info/onderwerp/dikkedarmkanker/cijfers-context/huidige-situatie#node-aantal-nieuwe-gevallen-van-dikkedarmkanker. Accessed June 26, 2017.
6. Yang Y, Wang G, He J, et al. Gender differences in colorectal cancer survival: A Meta-analysis. **Int J Cancer**. 2017.
7. Holme O, Schoen RE, Senore C, et al. Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials. **BMJ**. 2017;i6673.
8. Boeckx N, Koukakis R, Op de Beeck K, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. **Ann Oncol**. 2017;8:1862-1868.
9. Kim SE, Paik HY, Yoon H, et al. Sex- and gender-specific disparities in colorectal cancer risk. **World J Gastroenterol**. 2015;17:5167-5175.
10. de Jong RGPJ, Burden AM, de Kort S, et al. Impact of detection bias on the risk of gastrointestinal cancer and its subsites in type 2 diabetes mellitus. **Eur J Cancer**. 2017;61-71.
11. de Kort S, Simons CC, van den Brandt PA, et al. Diabetes mellitus type 2 and subsite-specific colorectal cancer risk in men and women: results from the Netherlands Cohort Study on diet and cancer. **Eur J Gastroenterol Hepatol**. 2016;8:896-903.
12. Gonzalez N, Prieto I, Del Puerto-Nevado L, et al. 2017 update on the relationship between diabetes and colorectal cancer: epidemiology, potential molecular mechanisms and therapeutic implications. **Oncotarget**. 2017;11:18456-18485.
13. Guraya SY. Association of type 2 diabetes mellitus and the risk of colorectal cancer: A meta-analysis and systematic review. **World J Gastroenterol**. 2015;19:6026-6031.
14. Luo W, Cao Y, Liao C, et al. Diabetes mellitus and the incidence and mortality of colorectal cancer: a meta-analysis of 24 cohort studies. **Colorectal Dis**. 2012;11:1307-1312.
15. Wu L, Yu C, Jiang H, et al. Diabetes mellitus and the occurrence of colorectal cancer: an updated meta-analysis of cohort studies. **Diabetes Technol Ther**. 2013;5:419-427.
16. Kramer HU, Schottker B, Raum E, et al. Type 2 diabetes mellitus and colorectal cancer: meta-analysis on sex-specific differences. **Eur J Cancer**. 2012;9:1269-1282.
17. Deng L, Gui Z, Zhao L, et al. Diabetes mellitus and the incidence of colorectal cancer: an updated systematic review and meta-analysis. **Dig Dis Sci**. 2012;6:1576-1585.
18. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. **J Natl Cancer Inst**. 2005;22:1679-1687.

19. PHARMO Institute for Drug Outcomes Research. www.pharmo.nl. Accessed June 21, 2017.
20. van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, et al. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. **Eur J Cancer**. 2010;2:395-404.
21. Kuiper JG, van Herk-Sukel MPP, van Wijngaarden RPT, et al. Unique opportunities to study the primary care of colorectal cancer. International Society For Pharmacoeconomics and Outcomes Research. Glasgow, Scotland: Value in Health 20: A741 (Abstract); 2017.
22. Statistics Netherlands. Statistics Netherlands. http://www.cbs.nl. Accessed March 18, 2015.
23. de Kort S, Masclee AAM, Sanduleanu S, et al. Higher risk of colorectal cancer in patients with newly diagnosed diabetes mellitus before the age of colorectal cancer screening initiation. **Sci Rep**. 2017;46527.
24. Diaz-Algorri Y, Lozada ME, Lopez SM, et al. Type 2 diabetes mellitus and colorectal neoplasia risk in Hispanics: a case-control study. **J Diabetes Complications**. 2015;4:502-507.
25. Woo H, Lee J, Lee J, et al. Diabetes Mellitus and Site-specific Colorectal Cancer Risk in Korea: A Case-control Study. **J Prev Med Public Health**. 2016;1:45-52.
26. Limburg PJ, Vierkant RA, Fredericksen ZS, et al. Clinically confirmed type 2 diabetes mellitus and colorectal cancer risk: a population-based, retrospective cohort study. **Am J Gastroenterol**. 2006;8:1872-1879.
27. Sikdar KC, Walsh SJ, Roche M, et al. Diabetes and sex-specific colorectal cancer risks in Newfoundland and Labrador: a population-based retrospective cohort study. **Can J Public Health**. 2013;2:e101-107.
28. Benedix F, Kube R, Meyer F, et al. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. **Dis Colon Rectum**. 2010;1:57-64.
29. Yuhara H, Steinmaus C, Cohen SE, et al. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? **Am J Gastroenterol**. 2011;11:1911-1921; quiz 1922.
30. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. **Ann Intern Med**. 1990;10:779-788.
31. Murphy G, Devesa SS, Cross AJ, et al. Sex disparities in colorectal cancer incidence by anatomic subsite, race and age. **Int J Cancer**. 2011;7:1668-1675.
32. Walraven I, van 't Riet E, Stehouwer CD, et al. Fasting proinsulin levels are significantly associated with 20 year cancer mortality rates. The Hoorn Study. **Diabetologia**. 2013;5:1148-1154.
33. van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. **Cancer Epidemiol Biomarkers Prev**. 2009;10:2569-2578.
34. Shin A, Joo J, Bak J, et al. Site-specific risk factors for colorectal cancer in a Korean population. **PLoS One**. 2011;8:e23196.
35. van 't Riet E, Alssema M, Rijkelijkhuizen JM, et al. Relationship between A1C and glucose levels in the general Dutch population: the new Hoorn study. **Diabetes Care**. 2010;1:61-66.

Supporting Information

Table S1 Codes used for exclusion and co-medication

	Coding system	Code	Description
Exclusion criteria			
Diagnosis of another type of diabetes than T2D	ICPC	T90.01	Type 1 Diabetes Mellitus
	Free text	-	Secondary diabetes
	Free text	-	MODY
Use of insulin	ATC	A10A	Insulins and analogues
Cancer diagnosis	ATC	L01	Antineoplastic agents
	ATC	L02B	Hormone antagonists and related agents
	ATC	L03AA	Colony stimulating factors (immunostimulants)
	ICPC	A79	Malignancy NOS
	ICPC	B72-B74	Hodgkin's disease/lymphoma/leukaemia/other malignant neoplasm blood
	ICPC	D74-D77	Malignant neoplasm stomach/colon/rectum/pancreas/digest other/digest NOS
	ICPC	N74	Malignant neoplasm nervous system
	ICPC	R84-R85	Malignant neoplasm bronchus/lung/respiratory, other
	ICPC	S77, excl. S77.01	Malignant neoplasm of skin, excluding 'in situ' and 'basal cell carcinoma'
	ICPC	T71	Malignant neoplasm thyroid
	ICPC	U75-U77	Malignant neoplasm of kidney/bladder/urinary other
	ICPC	W72	Malignant neoplasm relate to pregnancy
	ICPC	X75-X77	Malignant neoplasm cervix/breast female/genital other (f)
	ICPC	Y77-Y78	Malignant neoplasm prostate/genital other (m)
	ICD-O-3	C18-C20	Malignant neoplasm of colon/rectosigmoid junction/rectum
Co-medication			
Aspirin	ATC	B01AC06	Acetylsalicylic acid
		B01AC30	Clopidogrel/acetylsalicylic acid
		B01AC56	Acetylsalicylic acid/esomeprazole
		N02BA01	Acetylsalicylic acid
		N02BA51	Acetylsalicylic acid/ascorbic acid, acetylsalicylic acid/metoclopramide
Non-aspirin NSAIDs	ATC	M01A, excl. M01AX	Anti-inflammatory and antirheumatic products, non-steroids
Statins	ATC	C10AA	HMG CoA reductase inhibitors
Anti-hypertensives	ATC	C02	Antihypertensives
	ATC	C03	Diuretics
	ATC	C07	Beta blocking agents
	ATC	C08	Calcium channel blockers
	ATC	C09	Agents acting on the renin-angiotensin system
	HRT	ATC	G03C, G03F Oestrogens, progestogens and oestrogens in combination

Table S1 Number of CRC events and person years at risk among men and women with T2D and without diabetes

	Men				Women			
	T2D		no diabetes		T2D		no diabetes	
	N_{event}	$PY_{at\ risk}$	N_{event}	$PY_{at\ risk}$	N_{event}	$PY_{at\ risk}$	N_{event}	$PY_{at\ risk}$
colon and rectum	184	110,785	539	410,576	117	96,446	347	365,984
proximal	52	111,034	160	411,402	53	96,583	137	366,512
cecum	19	111,088	71	411,608	22	96,627	63	366,676
appendix	0	111,118	4	411, 737	0	96,657	3	366,773
ascending colon	23	111,082	43	411,659	17	96,630	35	366,693
hepatic flexure	6	111,106	11	411,718	8	96,646	16	366,738
transverse colon	4	111,111	31	411,660	6	96,650	20	366,742
distal	73	110,984	191	411,364	25	96,600	106	366,521
splenic flexure	1	111,117	10	411,738	6	96,644	10	366,760
descending colon	8	111,107	11	411,717	2	96,656	10	366,756
sigmoid colon	64	110,995	170	411,399	17	96,613	86	366,559
rectum	51	111,020	173	411,331	32	96,592	97	366,521

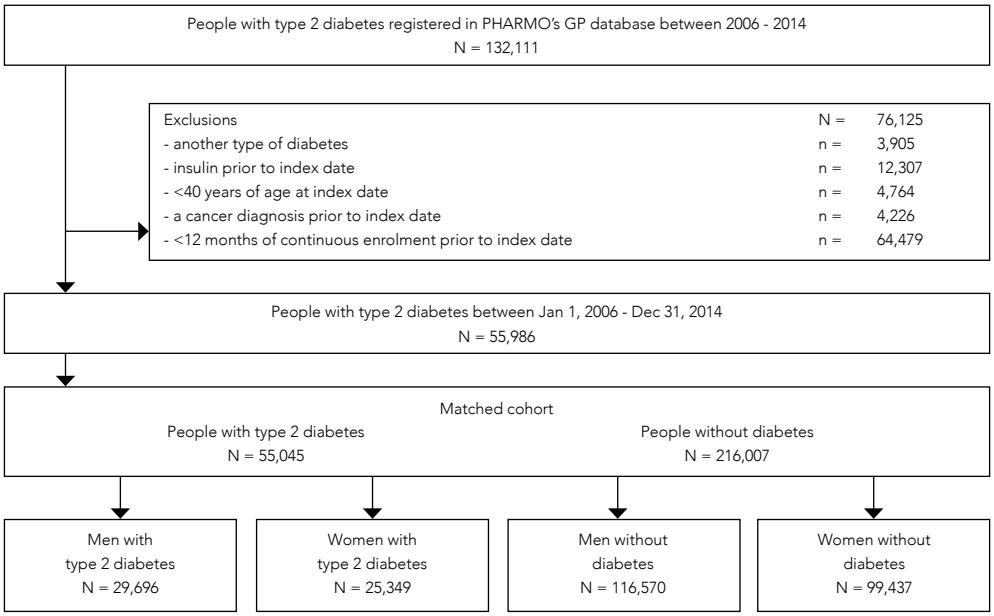


Figure S1 Flow chart of patient selection

INDEX

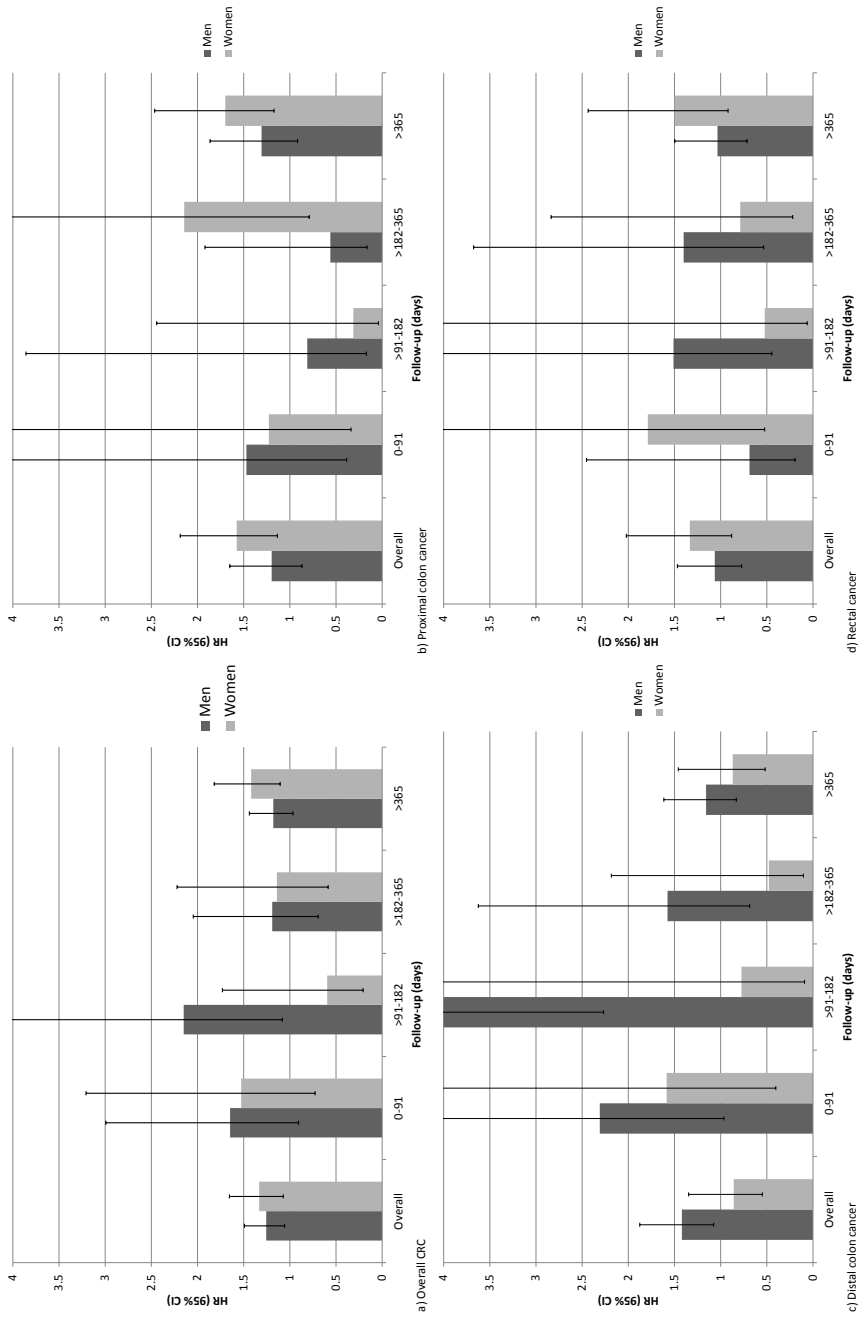


Figure S2 Difference between men and women in subsite CRC among people with type 2 diabetes compared to people with no diabetes stratified by follow-up period.

CHAPTER 9

Influence of matching and censoring on risk estimates: a case study in type 2 diabetes and cancer

Jetty A. Overbeek, Amber A.W.A. van der Heijden, Ron M.C. Herings, Giel Nijpels

Abstract

Background: Discussion regarding the association between type 2 diabetes mellitus (T2D) and cancer is still ongoing. However, there is less known whether this association is influenced by methodological considerations.

Objective: To investigate whether the association between T2D and cancer is influenced by study design or different censoring definitions.

Methods: A non-matched (Study I) and matched (Study II) design was used to study the association. For each design, three different approaches were performed using different criteria for the censoring or exclusion of people with incident diabetes during follow-up. Incidence rates were compared using competing-risk models. Hazard ratios (HRs) were determined per sex and adjusted for age, socioeconomic status (SES) and GP practice.

Results: Study I included >10,000 people with T2D and >210,000 people without DM, in Study II this was >15,000 people and >50,000 people. In both studies, using three different approaches, similar non-significant increased risks of breast cancer were found. Regarding prostate, all analyses in the non-matched cohort study resulted in a non-significant decreased risk, while in the matched cohort study all resulted in a significant decreased risk. A consistent increased risk of colorectal cancer was seen in all designs/approaches; non-significant in men and significant in women.

Conclusion: Matching or not matching and different censoring definitions did not influence the results regarding the association between diabetes and breast, prostate or colorectal cancer.

INDEX

Introduction

Prevalence of type 2 diabetes (T2D) is increasing worldwide. Due to the ageing population, better survival, more obesity and early detection of T2D it is expected that this prevalence will keep increasing.[1] The prevalence of cancer in western countries is increasing as well and currently the most frequently occurring cancers (excluding skin cancer) are breast and colorectal cancer among women and prostate and colorectal cancer among men.[2]
The number of publications related to the association between (drugs used to treat) T2D and cancer has increased rapidly in the last years. In an umbrella review of meta-analyses of observational studies on T2D and cancer,[3] it was concluded that, although the association has been extensively studied and strong claims of significance exist for most of the studied associations, only a minority of these associations have robust support without hints of bias. Most frequently the association between T2D and cancer incidence was studied by using a cohort design,[4-9] adjusted for relevant, known confounders. A widespread method to control for confounding in multiple areas of epidemiological studies is matching. However, it is less known to what extent matching influences results. An epidemiological case-control study did show that almost identical results were found irrespective of matching or not matching.[10] Furthermore, survival analyses are commonly applied to study cancer or other events of interest.[11] The primary aim of survival analysis is the modelling of 'time-to-event' data. However, many studies did not discuss the definition of end of follow-up (i.e., censoring) when performing survival analyses. When comparing people with T2D with people without T2D, people without T2D at baseline can develop T2D during follow-up. If this information is neglected a certain degree of exposure misclassification, i.e., information bias, occurs.[12] In addition, including only those controls not developing T2D during the study period is neglecting a key rule for performing a survival analysis; it is not allowed to use information at baseline that occurs in the future.[13]
The current study aims to investigate whether the association between T2D and cancer is affected by applying a matching design compared to the inclusion of all participating people in the control group (i.e., a non-matched design). Furthermore, the aim is to analyse the influence of different approaches for the censoring or exclusion of people with incident diabetes during follow-up on the results in a cohort study.

Materials and Methods

Data sources

Data were obtained from the PHARMO Database Network[14] linked on a patient-level to the Eindhoven area of the linked Netherlands Cancer Registry (E-NCR).[15] The PHARMO Database Network is a population-based network of electronic healthcare databases and combines data from different primary and secondary healthcare settings in the Netherlands. The NCR comprises information on newly diagnosed cancer patients in the Netherlands,

INDEX

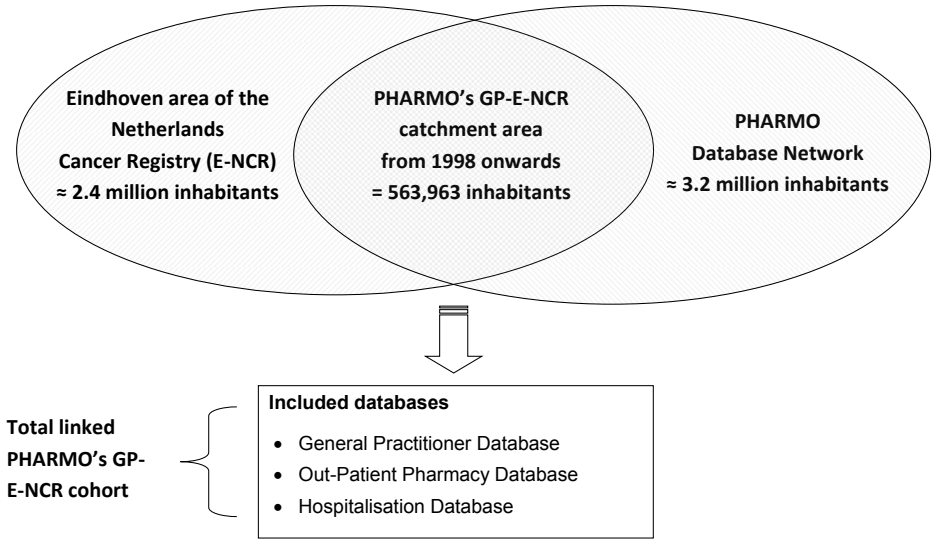
coded according to the WHO International Classification of Diseases for Oncology (ICD-O-3). The construct and validity of the PHARMO-E-NCR cohort are described elsewhere.[16]

Study design

A non-matched cohort study (Study I) as well as a matched cohort study (Study II) was performed. For Study I January 1, 2007 was used as index date for assessment of T2D status, resulting in a cohort with people with prevalent T2D. For Study II the date of the first sign of T2D was defined as the index date, resulting in a cohort with people with incident T2D.

Study population

The source population included all people in PHARMO's GP Database with a zip code similar to the zip codes belonging to the E-NCR catchment area (n=563,963, see Figure 1). The definitions of diagnoses used for selection of people with T2D and without diabetes are available in Supporting Table S1.



This Figure has been derived and adapted from a study on the PHARMO-ECR linkage.[16]

Figure 1 Number of inhabitants included in the PHARMO's GP-E-NCR catchment area

INDEX

Study I: non-matched cohort study
From the catchment area all people registered and alive in the database at January 1, 2007 were selected. People diagnosed with T2D prior or at January 1, 2007 were selected as people with T2D. People with no sign of T2D before or at January 1, 2007 were selected as people with no T2D. All people with another type of diabetes prior to January 1, 2007, aged <40 years at January 1, 2007 or diagnosed with any cancer prior to January 1, 2007 were excluded. People with T2D were required to have ≥12 months of continuous enrolment prior to the first sign of T2D to determine duration of T2D correctly. People with no diabetes were required to have ≥12 months of continuous enrolment prior to index date to ensure they did not have a diagnosis of diabetes.

Study II: matched cohort study
From the catchment area all people diagnosed with T2D between January 1, 1998 and December 31, 2011 were selected. The date of the first recorded episode for T2D, the second non-insulin antidiabetic drug prescription/dispensing, the first examination or the first hospitalization, whichever occurred first, was defined as the index date. People with another type of diabetes prior to the index date, people aged <40 years at index date, people with any cancer prior to index date, and people with <12 months of continuous enrolment prior to index date were excluded.
People with T2D were randomly matched (1:4) to controls (i.e., people with no T2D) on sex, year of birth (+/- 2 years), and GP practice. Furthermore, people were matched on year of start of data collection in the GP Database and in the Out-Patient Pharmacy Database. Matched controls received the same index date as the matched people with T2D. Controls had to be alive and known in the GP and Out-Patient Pharmacy Database at the time of the index date of the matched people with T2D, and were not allowed to have a diagnosis of diabetes at index date and could not be matched more than once.

Characteristics
For all people included in Study I and II the following was determined: age, sex, socioeconomic status (SES), available history and follow-up in the database, reason of end of follow-up and diabetes treatment in the first year of follow-up. SES was derived from Statistics Netherlands.[17] In Study I, duration of T2D was determined for people with T2D and defined as the time between the first sign of T2D in the database and January 1, 2007.

Cancer
During follow-up, the occurrence of the first cancer (ICD-O-3 C00-C97) was obtained from the E-NCR. When this cancer was a breast cancer (ICD-O-3 C50), a colorectal cancer (ICD-O-3 C18-C20) or a prostate cancer (ICD-O-3 C61) it was counted and used as outcome in the analyses.

INDEX

Statistical analysis

Characteristics of all included people were reported descriptively. Unadjusted incidence rates (IRs) for the different types of cancer were determined by dividing the total number of events by the total number of patient years at risk (summed number of years of follow-up). For all IRs the corresponding 95% confidence intervals (CI) were calculated. Because of the competing outcomes of other forms of cancer and death, IRs were compared between people with and without T2D using competing-risk regression models with other cancer and death as competing events. Hazard ratios (HRs) and their corresponding 95% CI were determined per sex and adjusted for age, SES and GP practice.

To study the consequences of censoring or excluding people with incident diabetes during follow-up, different approaches were performed:

1 Included people were censored at time of first occurring cancer, death, loss to follow-up in the PHARMO Database Network or end of study period (December 31, 2011), whichever occurred first.
2. Included people were censored at time of first occurring cancer, death, loss to follow-up in the PHARMO Database Network, end of study period or the diagnosis of any or another type of diabetes, whichever occurred first. For people with T2D this could be a recorded episode for T1DM, secondary diabetes or MODY. For people without diabetes this could be a recorded episode for T2D, T1DM, secondary diabetes or MODY.
3. People were followed as defined in 1, but people with T2D developing another type of diabetes and people without diabetes developing any type of diabetes anywhere during follow-up were both excluded.

As follow-up starts at the first sign of T2D in Study II and at January 1, 2007 in Study I, people in Study I had a longer duration of T2D at baseline than people in Study II. Therefore, an additional analysis was performed in Study I analysing the association between duration of T2D and the incidence of cancer.

All data were analysed using SAS programs organized within SAS Enterprise Guide version 4.3 (SAS Institute Inc., Cary, NC, USA) and conducted under Windows using SAS version 9.2. Competing-risk regression models were conducted using R version 3.1.3.

Results

Study population

Study I included >10,000 people with T2D and >210,000 people without diabetes as of January 1, 2007. Study II included >15,000 people with T2D between 1999 and 2011 and these were matched to >50,000 people without diabetes. For both studies, the number of people was slightly lower in approach 3, as people who developed any or another type of diabetes were excluded. In Study I, 31 (<0.5%) of the people with T2D developed another type of diabetes during follow-up and 10,016 (4%) of the people with no diabetes developed any type of diabetes during follow-up. For Study II these proportions were <0.5% and 10%,

INDEX

respectively. Supporting Figure S1 and S2 show the flow chart of patient selection for Study I and II, respectively.

Characteristics

Table 1 and Table 2 show the general characteristics of people with T2D (Table 1) and without diabetes (Table 2) for both Study I and Study II and the three different approaches for the censoring or exclusion of people.

People with T2D included in Study I were slightly older than people with T2D included in Study 2. No difference was observed between the three different approaches within a design. For SES and reason of end of follow-up no differences between Study I and Study II or between the three different approaches were observed. The history and follow-up in the database differed slightly, probably because of the different definitions of index date between Study I and Study II. No differences were observed between the different approaches within a design. The use of anti-diabetic treatment differed between Study I and Study II. People with T2D in Study I more often used anti-diabetics (65%) than people with T2D in Study II (51%). This finding has probably to do with the fact that Study I included people with prevalent T2D, while Study II included people with incident T2D.

People without diabetes included in Study I were younger, had a shorter follow-up duration in the database and less often developed DM during follow-up (approach 2) than people without diabetes included in Study II. For none of the characteristics there were differences observed between the three different approaches within a design.

Cancer

Incidence rates

Table 3 and Table 4 present the IRs with 95% CI and HRs with 95% CI for Study I and Study II for the three different analyses, respectively. In both studies, the different approaches for censoring or exclusion of people with incident diabetes during follow-up did not alter the IRs notably. Among both people with T2D and without diabetes, IRs for breast and prostate cancer were (slightly) higher in Study II than in Study I. For colorectal cancer, IRs among people with T2D were higher in Study I than in Study II, while IRs among people with no diabetes were higher in Study II than in Study I.

As Study I mainly included people with prevalent T2D and Study II included people with incident T2D, duration of T2D might explain the differences in IRs between the two studies. When including only people with T2D from Study I with T2D duration <1 year (i.e., people with incident T2D), IRs of the different cancers were more comparable to the IRs of Study II, except for prostate cancer. The IRs per 100 person-years (PY) among people with incident T2D in Study I were: 0.27 for breast cancer, 0.20 for prostate cancer, 0.16 for colorectal cancer among women and 0.18 for colorectal cancer among men.

INDEX

Table 1 General characteristics of people with T2D for Study I and Study II and the three different approaches for the censoring or exclusion of people

	Study I			Study II		
	Approach 1* N = 10,779 n (%)	Approach 2** N = 10,779 n (%)	Approach 3† N = 10,748 n (%)	Approach 1* N = 18,369 n (%)	Approach 2** N = 18,369 n (%)	Approach 3† N = 17,971 n (%)
General characteristics						
Age (years), mean ± SD	63.9 ± 10.8	63.9 ± 10.8	63.9 ± 10.8	62.0 ± 10.6	62.0 ± 10.6	61.9 ± 10.6
Gender male, n (%)	51	51	51	52	52	52
SES						
low	4,357 (40)	4,357 (40)	4,351 (40)	6,992 (38)	6,992 (38)	6,810 (38)
normal	3,337 (31)	3,337 (31)	3,328 (31)	5,815 (32)	5,815 (32)	5,725 (32)
high	2,077 (19)	2,077 (19)	2,071 (19)	3,768 (21)	3,768 (21)	3,680 (20)
unknown	1,008 (9)	1,008 (9)	998 (9)	1,794 (10)	1,794 (10)	1,756 (10)
History in database (years), mean ± SD	7.9 ± 2.1	7.9 ± 2.1	7.9 ± 2.1	7.1 ± 3.5	7.1 ± 3.5	7.2 ± 3.5
Follow-up in database (years), mean ± SD	4.8 ± 0.7	4.7 ± 0.9	4.7 ± 0.9	5.3 ± 3.2	5.3 ± 3.2	5.2 ± 3.2
Reason of end of follow-up						
Cancer	576 (5)	576 (5)	576 (5)	990 (5)	988 (5)	956 (5)
Death	493 (5)	492 (5)	492 (5)	746 (4)	741 (4)	720 (4)
Loss to follow-up	170 (2)	170 (2)	170 (2)	238 (1)	238 (1)	232 (1)
End of study period	9,540 (89)	9,510 (88)	9,510 (88)	16,395 (89)	16,345 (89)	16,063 (89)
DM‡	n.a.	31 (<0.5)	n.a.	n.a.	57 (<0.5)	n.a.
Anti-diabetic treatment$						
No3,748 (35)	3,748 (35)	3,735 (35)	9,056 (49)	9,056 (49)	8,846 (49)	
MET	2,777 (26)	2,777 (26)	2,777 (26)	5,402 (29)	5,402 (29)	5,313 (30)
SU 897 (8)	897 (8)	897 (8)	1,458 (8)	1,458 (8)	1,422 (8)	
MET + SU	2,241 (21)	2,241 (21)	2,239 (21)	1,829 (10)	1,829 (10)	1,790 (10)
MET + INS	176 (2)	176 (2)	170 (2)	66 (<0.5)	66 (<0.5)	62 (<0.5)
MET + SU + INS	204 (2)	204 (2)	201 (2)	89 (<0.5)	89 (<0.5)	84 (<0.5)
INS	138 (1)	138 (1)	134 (1)	33 (<0.5)	33 (<0.5)	28 (<0.5)
Other	598 (6)	598 (6)	595 (6)	436 (2)	436 (2)	426 (2)
Diabetes duration (years)						
Mean ± SD	3.0 ± 2.1	3.0 ± 2.1	3.0 ± 2.1	n.a.	n.a.	n.a.

Abbreviations: SD, standard deviation; MET, metformin; SU, sulfonylureas; INS, insulin; n.a., not applicable; *people were censored at time of death, loss to follow-up or end of study period; **people were censored at time of death, loss to follow-up, end of study period or the diagnosis of a type of diabetes; †people developing any or another or a type of diabetes were excluded; ‡people with T2D who develop another type of DM and people with no DM who develop any type of DM; $determined in the first year of follow-up.

Table 2 General characteristics of people without diabetes for Study I and Study II and the three different approaches for the censoring or exclusion of people

	Study I			Study II		
	Approach 1* N = 224,364 n (%)	Approach 2** N = 224,364 n (%)	Approach 3† N = 214,348 n (%)	Approach 1* N = 58,880 n (%)	Approach 2** N = 58,880 n (%)	Approach 3† N = 52,933 n (%)
General characteristics						
Age (years), mean ± SD	55.8 ± 11.4	55.8 ± 11.4	55.6 ± 11.4	60.8 ± 10.2	60.8 ± 10.2	60.6 ± 10.3
Gender male, n (%)	48	48	48	51	51	51
SES						
low	57,050 (25)	57,050 (25)	53,445 (25)	17,859 (30)	17,859 (30)	15,524 (29)
normal	75,269 (34)	75,269 (34)	72,072 (34)	19,186 (33)	19,186 (33)	17,305 (33)
high	70,388 (31)	70,388 (31)	68,209 (32)	15,986 (27)	15,986 (27)	14,811 (28)
unknown	21,657 (10)	21,657 (10)	20,622 (10)	5,849 (10)	5,849 (10)	5,293 (10)
History in database (years), mean ± SD	7.2 ± 2.3	7.2 ± 2.3	7.2 ± 2.3	7.2 ± 3.5	7.2 ± 3.5	7.4 ± 3.5
Follow-up in database (years), mean ± SD	4.9 ± 0.5	4.7 ± 0.9	4.8 ± 0.7	5.4 ± 3.2	5.0 ± 3.1	5.2 ± 3.1
Reason of end of follow-up						
Cancer	7,041 (3)	6,742 (3)	6,742 (3)	2,569 (4)	2,260 (4)	2,248 (4)
Death	3,816 (2)	3,591 (2)	3,591 (2)	1,317 (2)	1,158 (2)	1,157 (2)
Loss to follow-up	4,038 (2)	3,956 (2)	3,956 (2)	655 (1)	622 (1)	622 (1)
End of study period	209,469 (93)	200,059 (89)	200,059 (93)	54,339 (92)	49,060 (83)	48,906 (92)
DM‡	n.a.	10,016 (4)	n.a.	n.a.	5,780 (10)	n.a.

Abbreviations: SD, standard deviation; *people were censored at time of death, loss to follow-up or end of study period; **people were censored at time of death, loss to follow-up, end of study period or the diagnosis of a type of diabetes; †people developing any or another or a type of diabetes were excluded; ‡people with T2D who develop another type of DM and people with no DM who develop any type of DM.

Hazard ratios

Figure 2 shows the HRs with 95% CI for Study I and Study II for the three different follow-up approaches.

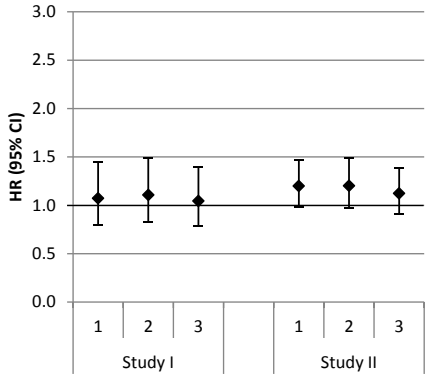


Figure 2a: Breast cancer

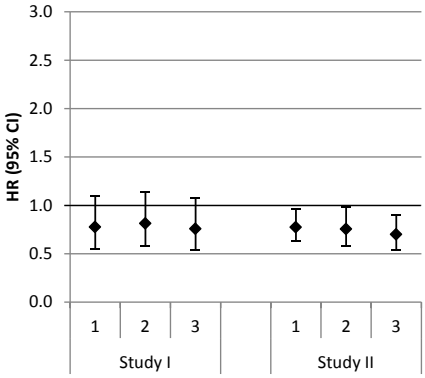


Figure 2b: Prostate cancer

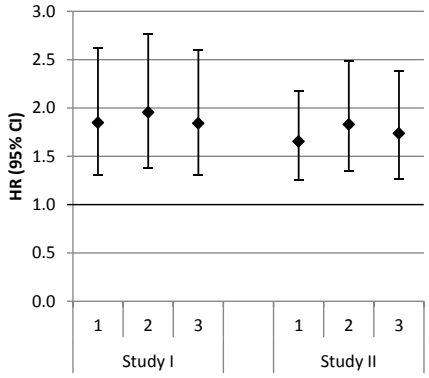


Figure 2c: Colorectal cancer among women

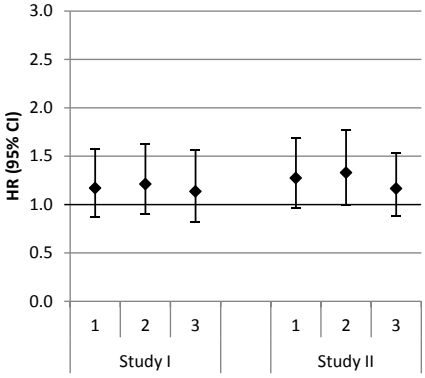


Figure 2d: Colorectal cancer among men

1 = approach 1: people were censored at time of first occurring cancer, death, loss to follow-up or end of study period, whichever occurred first; 2 = approach 2: people were censored at time of first occurring cancer, death, loss to follow-up, end of study period or the diagnosis of any or another type of diabetes, whichever occurred first; 3 = approach 3: people were followed as defined in approach 1, but people with T2D developing another type of diabetes and people without diabetes developing any type of diabetes anywhere during follow-up were both excluded. Study I = non-matched cohort study; Study II = matched-cohort study.

Figure 2 Hazard ratios (95% CI) for breast, prostate and colorectal cancer for people with T2D versus people without diabetes for Study I and Study II and the three different approaches for the censoring or exclusion of people

INDEX

Regarding breast cancer, in both studies, all analyses showed a non-significant increased risk of breast cancer in women with T2D compared to women without diabetes (Figure 2a). The risk estimates in Study II were slightly higher than in Study I. Regarding prostate cancer, Study I resulted in a non-significant decreased risk, while Study II resulted in a significant decreased risk (Figure 2b). This was similar across all three analyses. For colorectal cancer, a consistent increased risk was seen in all analyses; statistically significant among women (Figure 2c) and non-significant for men (Figure 2d).
In Study I follow-up started at January 1, 2007 (at January 1, 2007 mean duration of T2D was 4.1 years) and in Study II follow-up started at the first sign of T2D. When performing the additional analysis in Study I investigating the association between duration of T2D and the incidence of cancer, the IRs and HRs in people with duration of T2D <1 year went towards the IRs and HRs from Study II for colorectal cancer, but not for breast and prostate cancer. This might implicate that duration of T2D plays a more important role in colorectal cancer than in breast and prostate cancer.

Discussion

This epidemiological study investigated the relationship between T2D and the incidence of cancer using different study designs and different follow-up approaches in the same cohort. A statistically non-significant increased risk of breast cancer in women with T2D was found in all analyses. For prostate cancer, a decreased risk among men with T2D was found. Regarding colorectal cancer, we found a consistent increased risk of colorectal cancer in people with T2D, but this was only statistically significant for women. Differences between sex regarding colorectal cancer appear to be more important than initially was thought. [18-21]
The non-matched and matched design and the different censoring definitions did not alter the results materially.
To our knowledge this is the first cohort study investigating the influence of applying a matching and a non-matching design on the relationship between T2D and cancer incidence. IRs and HRs were quite similar between the non-matched and matched cohort study. Only the HRs for breast cancer among women were consistently somewhat higher in the matched cohort study than in the non-matched study. The role of matching in epidemiological research is somewhat controversial.[10] Matching is sometimes routinely performed, even when the matched variables are not regarded as confounders nor extremely distributed. However, matching can prevent confounding by the matched variables.[22] In our study the matched variables also included GP practice, which might correct for unmeasured variables like treatment-behaviour of the GP.
This is also the first study to our knowledge investigating the effect on results when using different approaches for the censoring or exclusion of people with incident diabetes during follow-up. Again, IRs and HRs did not differ between the three different approaches. HRs were slightly higher in the second follow-up approach, where people were censored when they

INDEX

Table 3 Event rates among people with T2D and without diabetes - non-matched cohort study (Study I)

	People with T2D				People without diabetes				People with T2D vs. people without diabetes	
	$N_{at\ risk}$	$PY_{at\ risk}$	N_{event}	IR/100 PY (95% CI)	$N_{at\ risk}$	$PY_{at\ risk}$	N_{event}	IR/100 PY (95% CI)	HR	95% CI
Breast cancer										
Approach 1	5,287	25,052	65	0.26 (0.20-0.33)	117,011	568,301	1,228	0.22 (0.20-0.23)	1.07	(0.80-1.44)
Approach 2	5,287	25,017	65	0.26 (0.20-0.33)	117,011	556,581	1,188	0.21 (0.20-0.23)	1.11	(0.82-1.49)
Approach 3	5,274	24,987	65	0.26 (0.20-0.33)	112,310	545,311	1,188	0.22 (0.21-0.23)	1.04	(0.78-1.39)
Prostate cancer										
Approach 1	5,492	25,969	66	0.25 (0.20-0.32)	107,353	519,375	1,041	0.20 (0.19-0.21)	0.78	(0.55-1.09)
Approach 2	5,492	25,917	66	0.25 (0.20-0.32)	107,353	506,137	998	0.20 (0.19-0.21)	0.81	(0.58-1.14)
Approach 3	5,474	25,881	66	0.26 (0.20-0.32)	102,038	493,323	998	0.20 (0.19-0.22)	0.76	(0.54-1.08)
Colorectal cancer										
Women										
Approach 1	5,287	25,052	56	0.22 (0.17-0.29)	117,011	568 301	418	0.07 (0.07-0.08)	1.85	(1.30-2.62)
Approach 2	5,287	25,017	56	0.22 (0.17-0.29)	117,011	556 581	392	0.07 (0.06-0.08)	1.95	(1.38-2.76)
Approach 3	5,274	24,987	56	0.22 (0.17-0.29)	112,310	545 311	392	0.07 (0.06-0.08)	1.84	(1.30-2.60)
Men										
Approach 1	5,492	25,969	57	0.22 (0.17-0.28)	107,353	519 375	622	0.12 (0.11-0.13)	1.17	(0.87-1.57)
Approach 2	5,492	25,917	57	0.22 (0.17-0.28)	107,353	506 137	594	0.12 (0.11-0.13)	1.21	(0.90-1.62)
Approach 3	5,474	25,881	57	0.22 (0.17-0.29)	102,038	493 323	594	0.12 (0.11-0.13)	1.13	(0.82-1.56)

Abbreviations: T2D,type 2 diabetes mellitus; PY, person-years; IR, incidence rate; HR, hazard ratio; CI, confidence interval. Approach 1 = people were censored at time of first occurring cancer, death, loss to follow-up or end of study period, whichever occurred first. Approach 2 = people were censored at time of first occurring cancer, death, loss to follow-up, end of study period or the diagnosis of any or another type of diabetes, whichever occurred first; Approach 3 = people were followed as defined in approach 1, but people with T2D developing another type of diabetes and people without diabetes developing any type of diabetes anywhere during follow-up were both excluded. Study I = non-matched cohort study; Study II = matched-cohort study.

Table 4 Event rates among people with T2D and without diabetes - matched cohort study (Study II)

	People with T2D				People without diabetes				People with T2D s. people without diabetes	
	$N_{at\ risk}$	$PY_{at\ risk}$	N_{event}	IR/100 PY (95% CI)	$N_{at\ risk}$	$PY_{at\ risk}$	N_{event}	IR/100 PY (95% CI)	HR	95% CI
Breast cancer										
Approach 1	8,894	47,487	138	0.29 (0.24-0.34)	28,632	157,190	381	0.24 (0.22-0.27)	1.20	(0.98-1.47)
Approach 2	8,894	47,351	138	0.29 (0.24-0.34)	28,632	144,657	345	0.24 (0.21-0.27)	1.20	(0.97-1.49)
Approach 3	8,706	46,084	134	0.29 (0.24-0.34)	25,808	135,350	345	0.25 (0.23-0.28)	1.12	(0.91-1.39)
Prostate cancer										
Approach 1	9,475	49,303	131	0.27 (0.22-0.32)	30,248	161,408	473	0.29 (0.27-0.32)	0.77	(0.63-0.96)
Approach 2	9,475	49,151	131	0.27 (0.22-0.32)	30,248	147,843	430	0.29 (0.26-0.32)	0.76	(0.58-0.99)
Approach 3	9,265	47,804	124	0.26 (0.22-0.31)	27,125	137,791	427	0.31 (0.28-0.34)	0.70	(0.54-0.90)
Colorectal cancer										
Women										
Approach 1	8,894	47,487	90	0.19 (0.15-0.23)	28,632	157,190	166	0.11 (0.09-0.12)	1.65	(1.25-2.18)
Approach 2	8,894	47,351	90	0.19 (0.15-0.23)	28,632	144,657	138	0.10 (0.08-0.11)	1.83	(1.34-2.49)
Approach 3	8,706	46,084	87	0.19 (0.15-0.23)	25,808	135,350	138	0.10 (0.09-0.12)	1.74	(1.26-2.39)
Men										
Approach 1	9,475	49,303	92	0.19 (0.15-0.23)	30,248	161,408	242	0.15 (0.13-0.17)	1.27	(0.96-1.69)
Approach 2	9,475	49,151	91	0.19 (0.15-0.23)	30,248	147,843	205	0.14 (0.12-0.16)	1.33	(1.00-1.77)
Approach 3	9,265	47,804	87	0.18 (0.15-0.22)	27,125	137,791	204	0.15 (0.13-0.17)	1.16	(0.88-1.53)

Abbreviations: T2D,type 2 diabetes mellitus; PY, person-years; IR, incidence rate; HR, hazard ratio; CI, confidence interval. Approach 1 = people were censored at time of first occurring cancer, death, loss to follow-up or end of study period, whichever occurred first. Approach 2 = people were censored at time of first occurring cancer, death, loss to follow-up, end of study period or the diagnosis of any or another type of diabetes, whichever occurred first; Approach 3 = people were followed as defined in approach 1, but people with T2D developing another type of diabetes and people without diabetes developing any type of diabetes anywhere during follow-up were both excluded. Study I = non-matched cohort study; Study II = matched-cohort study.

developed any or another type of diabetes. Another study conducted a sensitivity analysis by excluding those control people who developed diabetes during the follow-up period.[23] This also resulted in similar results as the original results.
Although the three different approaches did not yield different results, approach 2 is methodologically seen the most sound approach; exposure misclassification (present in approach 1) is decreased and no information that occurs in the future is used at baseline (as done in approach 3). However, as change of exposure during follow-up is not always available; the current study shows that another approach (approach 1 or 3) does not influence the association substantially.
This study was based on a large database network with an accurate linkage.[16, 24] The IRs for breast, colorectal and prostate cancer found in our study are similar to the IRs published by the Dutch National Public Health Compass.[25-27] Also the found associations between T2D and breast,[5-7, 9, 28] colorectal[6, 8, 29] and prostate cancer[4, 30, 31] are comparable to literature. The absence of statistical significance in our results might be due to lack of statistical power because of a smaller sample size.
This study has also some limitations. First, no corrections were made for confounders such as BMI. Unfortunately, information regarding BMI is not complete, especially not among people with no DM. Furthermore, follow-up duration was only about 5 years, which might be too short to see associations between T2D and cancer. Although these limitations might have influenced the point-estimates and the significance-levels, it is not assumed that this would differ between the non-matched and the matched cohort study. Therefore, we assumed that these limitations do not influence the conclusions of the study.
The reason for finding no impact on point-estimates when censoring or excluding people might also be explained by the relatively low number of people who developed any or another type of diabetes during follow-up (e.g. the low incidence of (any type of) diabetes in the five years of follow-up). It might be interesting to perform a similar study for an association in which the prevalence and incidence of the outcome of interest is higher.

Conclusions

T2D is associated with an increased risk of breast and colorectal cancer, but with a decreased risk of prostate cancer. These findings are not influenced by using a non-matched or non-matched design and not by censoring or excluding people developing diabetes during follow-up. However, the results of this study provide relevant background information regarding possible biases when interpreting other studies focussing on the association between T2D and cancer.

INDEX

References

1. Rijksinstituut voor Volksgezondheid en Milieu. Neemt het aantal mensen met diabetes mellitus toe of af? Available from: http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/endocriene-voedings-en-stofwisselingsziekten-en-immuniteitsstoornissen/diabetes-mellitus/trend/. Accessed 15 February 2016, 2016.
2. Integraal Kankercentrum Nederland. Figures regarding cancer. Available from: http://www.cijfersoverkanker.nl/. Accessed 15 February 2016 2016.
3. Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JP. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. **BMJ**. 2015; 350: g7607.
4. Bansal D, Bhansali A, Kapil G, Undela K, Tiwari P. Type 2 diabetes and risk of prostate cancer: a meta-analysis of observational studies. **Prostate Cancer Prostatic Dis**. 2013; 16: 151-158, S151.
5. Boyle P, Boniol M, Koechlin A, Robertson C, Valentini F, Coppens K, et al. Diabetes and breast cancer risk: a meta-analysis. **Br J Cancer**. 2012; 107: 1608-1617.
6. De Bruijn KM, Arends LR, Hansen BE, Leeflang S, Ruiter R, van Eijck CH. Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. **Br J Surg**. 2013; 100: 1421-1429.
7. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. **Int J Cancer**. 2007; 121: 856-862.
8. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. **J Natl Cancer Inst**. 2005; 97: 1679-1687.
9. Liao S, Li J, Wei W, Wang L, Zhang Y, Li J, et al. Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature. **Asian Pac J Cancer Prev**. 2011; 12: 1061-1065.
10. Faresjo T, Faresjo A. To match or not to match in epidemiological studies--same outcome but less power. **Int J Environ Res Public Health**. 2010; 7: 325-332.
11. Noordzij M, Leffondre K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? **Nephrol Dial Transplant**. 2013; 28: 2670-2677.
12. Bouter LM, van Dongen MCJM, Zielhuis GA. Epidemiologisch onderzoek: opzet en interpretatie: Bohn Stafleu van Loghum; 2010.
13. Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model (Statistics for Biology and Health). Dietz K, Gail M, Krickeberg K, Samet J, Tsiatis A, editors. New York: Springer; 2001.
14. PHARMO Institute for Drug Outcomes Research. PHARMO Institute for Drug Outcomes Research. Available from: http://www.pharmo.com. Accessed 12 February 2016, 2016.
15. Integraal Kankercentrum Nederland. Netherlands Comprehensive Cancer Organisation. Available from: http://www.iknl.nl. Accessed 15 February 2016, 2016.

INDEX

16. van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, Vreugdenhil G, Pruijt JF, Coebergh JW, et al. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. **Eur J Cancer**. 2010; 46: 395-404.
17. Statistics Netherlands. Statistics Netherlands. Available from: http://www.cbs.nl. Accessed 18 March 2015, 2015.
18. de Kort S, Simons CC, van den Brandt PA, Goldbohm RA, Arts IC, de Bruine AP, et al. Diabetes mellitus type 2 and subsite-specific colorectal cancer risk in men and women: results from the Netherlands Cohort Study on diet and cancer. **Eur J Gastroenterol Hepatol**. 2016; 28: 896-903.
19. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Preliminary communication: glycated hemoglobin, diabetes, and incident colorectal cancer in men and women: a prospective analysis from the European prospective investigation into cancer-Norfolk study. **Cancer Epidemiol Biomarkers Prev**. 2004; 13: 915-919.
20. Nilsen TI, Vatten LJ. Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis. **Br J Cancer**. 2001; 84: 417-422.
21. Will JC, Galuska DA, Vinicor F, Calle EE. Colorectal cancer: another complication of diabetes mellitus? **Am J Epidemiol**. 1998; 147: 816-825.
22. Mansournia MA, Hernan MA, Greenland S. Matched designs and causal diagrams. **Int J Epidemiol**. 2013; 42: 860-869.
23. Chen HF, Chang YH, Ko MC, Li CY. A large scale population-based cohort study on the risk of ovarian neoplasm in patients with type 2 diabetes mellitus. **Gynecol Oncol**. 2014; 134: 576-580.
24. Herings RMC, Pedersen L. Pharmacy-based Medical Record LInkage Systems. In: Strom BL, Kimmel SE, Hennessy, (eds). Pharmacy-based Medical Record LInkage Systems. 5th ed. Oxford: Wiley Blackwell; 2012. 270-286.
25. Gommer AM, Poos MJJC. Hoe vaak komt borstkanker voor en hoeveel mensen sterven eraan? Available from: http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/kanker/borstkanker/omvang/. Accessed 10 September 2016, 2016.
26. Poos MJJC, Gommer AM. Hoe vaak komt dikkedarmkanker voor en hoeveel mensen sterven eraan? Available from: http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/kanker/dikkedarmkanker/beschrijving/. Accessed 10 September 2016, 2016.
27. Gommer AM, Horenblas S. Hoe vaak komt prostaatkanker voor, hoeveel mensen sterven eraan en neemt dit toe of af? Available from: http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/kanker/prostaatkanker/omvang/. Accessed 10 September 2016, 2016.
28. Hardefeldt PJ, Edirimanne S, Eslick GD. Diabetes increases the risk of breast cancer: a meta-analysis. **Endocr Relat Cancer**. 2012; 19: 793-803.

INDEX

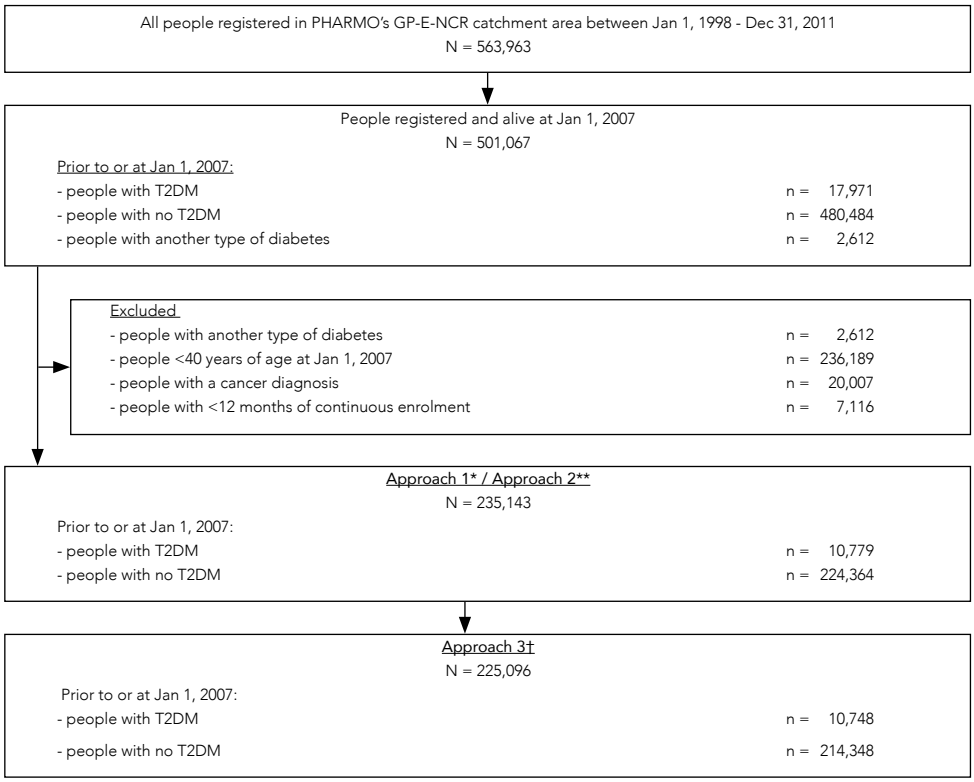
29. Jiang Y, Ben Q, Shen H, Lu W, Zhang Y, Zhu J. Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. **Eur J Epidemiol**. 2011; 26: 863-876.
30. Jian Gang P, Mo L, Lu Y, Runqi L, Xing Z. Diabetes mellitus and the risk of prostate cancer: an update and cumulative meta-analysis. **Endocr Res**. 2015; 10.3109/07435800.2014.934961.
31. Xu H, Mao SH, Ding GX, Ding Q, Jiang HW. Diabetes mellitus reduces prostate cancer risk - no function of age at diagnosis or duration of disease. **Asian Pac J Cancer Prev**. 2013; 14: 441-447.

Supporting Information

Table S1 Definitions of diagnoses used for selection of people with T2D and without diabetes

Definition	Codes	
T2D		
Recorded episode for T2D	ICPC	T90.02
≥2 prescriptions/dispensings for drugs used in diabetes, excluding insulins, within a 6 month period	ATC	A10B
Examination 'T2D diagnosed previously'	NHG	1647
Hospitalisation with a diagnosis for T2D	ICD-9-CM	250
No sign of T2D		
None of the definitions as defined under 'T2D'		
Another type of diabetes		
Recorded episode for T1D	ICPC	T90.01
Prescription/dispensing for insulin	ATC	A10A
Secondary diabetes, defined as a relevant description regarding secondary diabetes in a recorded episode (no specific code available)	n.a.	n.a.
Indication of MODY, defined as relevant description regarding MODY in a recorded episode (no specific code available)	n.a.	n.a.
Cancer		
Cancer diagnosis in the E-NCR	ICD-O-3	C00-C80.9
Hospitalisation with a diagnosis for malignant neoplasm	ICD-9-CM	140-209.3, 235-239
Hospitalisation for encounter for chemotherapy and immunotherapy for neoplastic conditions	ICD-9-CM	V58.1
Prescription/dispensing for cancer medication	ATC	L01A, L01C, L02B, L01BB, L01BC, L03AA

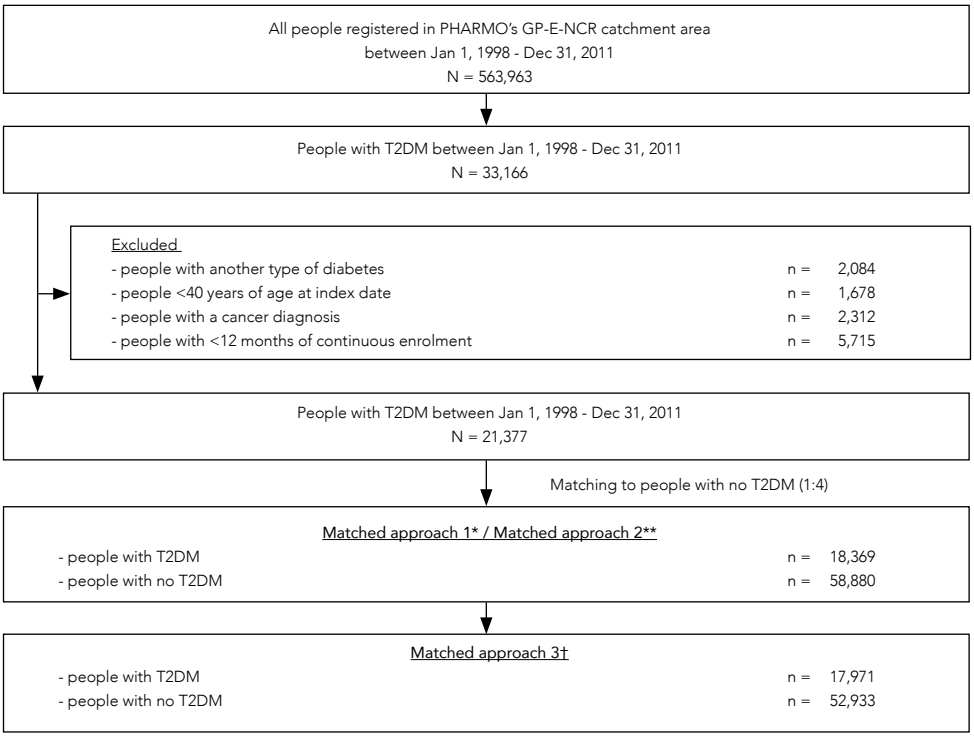
T2D, type 2 diabetes mellitus; T1D, type 1 diabetes mellitus; MODY, maturity-onset diabetes of the young; E-NCR, Eindhoven area of the linked Netherlands cancer registry; ICPC, international classification of primary care; ATC, anatomical therapeutic chemical; NHG, Nederlands Huisartsen Genootschap; ICD-9-CM, international classification of disease, ninth revision, clinical modification; ICD-O-3, international classification of diseases for oncology, 3rd edition.



*People were censored at time of death, loss to follow-up or end of study period; **People were censored at time of death, loss to follow-up, end of study period or the diagnosis of a type of diabetes; †People developing any or another or a type of diabetes were excluded.

Figure S1 Flow chart of patient selection - non-matched cohort study (Study I)

INDEX



*People were censored at time of death, loss to follow-up or end of study period; **People were censored at time of death, loss to follow-up, end of study period or the diagnosis of a type of diabetes; †People developing any or another or a type of diabetes were excluded.

Figure S2 Flow chart of patient selection - matched cohort study (Study II)

INDEX

INDEX

CHAPTER 10

General discussion

INDEX

The number of people with diabetes is growing and the number of people treated with newer blood glucose lowering drugs is also expected to grow. Population-based evidence, next to evidence from randomised controlled trials (RCTs), supports the decision making process of health care professionals treating people with diabetes. In addition, more insight into the effectiveness and safety of blood glucose lowering drugs in a daily practice setting is needed. These parameters are thoroughly studied in RCTs, but daily clinical practice differs from the experimental setting with respect to heterogeneity of patients, their age, treatments and co-morbidities. Furthermore, important side effects may not be detectable in clinical trials since the frequency of many adverse events is low and adverse effects of therapies may occur many years after drug administration. One of the major discussions in the field of diabetes is whether the association between diabetes and/or blood glucose lowering drugs and cancer is causal.[1-7]

The PHARMO DIAbetes, MANagement and Treatment (DIAMANT) cohort is a unique and detailed database containing all people with diabetes from the PHARMO Database Network. The PHARMO Database Network is a population-based network of electronic healthcare databases combining data from different primary and secondary healthcare settings in the Netherlands. Detailed information on the methodology and the validation of the used record linkage method can be found elsewhere.[8, 9] The network covers a historical, yearly updated anonymized population including more than 7 million individuals (3 million cross-sectional) provided by the STIZON foundation.[10] Data originate from electronic health records of thousands of GPs, hundreds of pharmacies and dozens of clinical laboratories from 1998 onwards and are linked to national registries on a project basis. These national registries include hospital admissions (Landelijke Basisregistratie Ziekenhuiszorg),[11] the nationwide registry of histo- and cytopathology in the Netherlands[10] and the Netherlands Cancer Registry (NCR)[12.]

This thesis aimed to gain more insight into type 2 diabetes (T2D), its pharmacological treatment, and its associations with cancer in real-world clinical practice using data from the PHARMO DIAMANT cohort.

Main findings

Prevalence of diabetes

In the period 1999-2014, the prevalence of diabetes increased from 1.8% to 4.9% in the Netherlands and almost half of this increase has to be explained by other factors than demographic changes **(Chapter 2)**. Unfortunately, these other factors could not be studied, as historical information, on for example body mass index (BMI), was not consistently available throughout the study period. However, other observational data from the Netherlands showed that the proportion of people with obesity almost tripled during 1981-2017 (from

INDEX

5.4% to 14.2%).[13] Although a direct relationship between the increased prevalence of diabetes and overweight could not be proven, the seemingly unstoppable weight gain in the Dutch society in the past decades is likely to be an important explanatory factor for the observed increase in the prevalence of diabetes in the past 15 years.

Treatment of people with type 2 diabetes

With the increasing prevalence of diabetes, the number of people receiving blood glucose lowering drugs naturally also increases. Results from a multi-database study across five countries in Europe showed the dominance of treatment guidelines for T2D **(Chapter 3)**. The acting Dutch general practitioner (GP) guideline for T2D during the study period advices a step-wise approach starting with metformin.[14] It is recommended to intensify treatment if the disease progresses or treatment fails to achieve or sustain glycaemic control. Following steps include adding a sulfonylurea derivative (SU) and adding insulin. The use of newer incretin-based blood glucose lowering drugs (dipeptidyl peptidase-4 [DPP-4] inhibitors and glucagon-like peptide-1 [GLP-1] receptor agonists) was during the study period not supported by The Dutch College of GPs,[15] until July 2018. During the study period (2007-2011), metformin was the most common initial treatment and after initial therapy, most patients switched to a combination of metformin and an SU. Furthermore, treatment with newer incretin-based blood glucose lowering drugs was uncommon in the Netherlands compared to the other European countries.

In **Chapter 4**, liraglutide showed, compared with basal insulin supported oral therapy (BOT), to be associated with significant reductions in HbA_{1c}, weight and BMI over a period of 12 months after treatment initiation. In both cohorts, the fluctuations in systolic blood pressure (BP), diastolic BP, and lipids were small, and no differences were observed between the cohorts. The longitudinal nature of the PHARMO DIAMANT cohort allowed us to follow patients over approximately 10 years including multiple measurements from each person.

Glycaemic exposure and micro- and macrovascular complications

Also in **Chapter 5**, multiple measurements per person were used to study the relationship between different measures of glycaemic exposure and micro- and macrovascular complications. While many studies use an HbA_{1c} measurement at a single point in time to assess the relation between HbA_{1c} and outcome, this study determined the association between single point (HbA_{1c} at index, time-dependent HbA_{1c}), exponential moving average and area under the curve (AUC) measurements and micro- and macrovascular complications. The AUC measurement (e.g., glycaemic burden) appeared to be more strongly associated with both micro- and macrovascular complications than the other measures.

Association between diabetes and/or blood glucose lowering drugs and cancer

Several blood glucose lowering drugs have been associated with cancer (e.g., metformin,[16] insulin[17] and incretin-based drugs[18]). However, the debate as to whether or not diabetes

INDEX

and/or blood glucose lowering drugs influence the risk of cancer is still ongoing. In Chapter 6-8 we aimed to further disentangle these associations.

DPP-4 inhibitors
Based on the review of published epidemiological studies and randomised clinical trials **(Chapter 6)**, we also did not find evidence that DPP-4 inhibitors were associated with an increased risk of site-specific cancer. Many studies suffered from methodological limitations and the duration of the included studies was relatively short. Our conclusions were confirmed by recently published epidemiological studies.[19-24] Currently, no sufficient evidence supports a relationship between the use of DPP-4 inhibitors and site-specific cancer.

Insulin analogues
Although the possible mechanism to explain an association between insulin (analogues) treatment and an increased cancer risk is rather plausible, there is currently little to no evidence that insulin (analogues) treatment is associated with the risk of breast cancer.[25] Although it is still possible that insulin (analogues) treatment influences the progression of breast cancer, epidemiological evidence regarding this association is also lacking. These type of studies require long follow-up and large cohorts with detailed information on both medication use and breast cancer. We studied the association between insulin (analogues) treatment and specific breast cancer characteristics in a nested case-control study in a breast cancer cohort (N=33,377) **(Chapter 7)**. Our study revealed that T2D, and not the use of insulin (analogues), was associated with developing more aggressive breast cancer tumours.

Women with T2D were also at risk to be diagnosed with proximal colon cancer compared to women without diabetes. This increased risk was higher among women than among men, while men with T2D compared to men without diabetes were at higher risk for developing distal colon cancer than women with T2D compared to women without diabetes **(Chapter 8)**. These findings are consistent with existing literature.[26-30] Apparently, the association between diabetes and colorectal cancer (CRC) varies per location of CRC and per sex.
In conclusion, after controlling for bias and confounding factors, we did not find evidence that blood glucose lowering drugs were associated with an increased risk of developing cancer. We found limited evidence that diabetes as disease is a risk factor for cancer. We found compelling evidence that having diabetes, as a disease, worsens the severity of breast cancer among patients who have cancer. If so, studies regarding blood glucose lowering drugs should be interpreted very cautiously as the entanglement of both diseases might severely confound risk assessment of blood glucose lowering drugs.

INDEX

Methodological considerations

Study population

Data for the studies in this thesis were obtained from the PHARMO DIAMANT cohort which is based on the PHARMO Database Network. The PHARMO Database Network is a population-based network of electronic healthcare databases combining data from different primary and secondary healthcare settings in the Netherlands. Detailed information on the methodology and the validation of the used record linkage method can be found elsewhere.[8, 9] The network covers a historical, yearly updated anonymized population including more than 7 million individuals (3 million cross-sectional) provided by the STIZON foundation.[10] Data originate from electronic health records of thousands of GPs, hundreds of pharmacies and dozens of clinical laboratories from 1998 onwards and are linked to national registries on a project basis. These national registries include hospital admissions (Landelijke Basisregistratie Ziekenhuiszorg),[11] the nationwide registry of histo- and cytopathology in the Netherlands10 and the Netherlands Cancer Registry (NCR)[12].

People in the PHARMO DIAMANT cohort can be included because of an indication of diabetes in primary care (GP Database) or because of a drug dispensing for a blood glucose lowering drug. Especially the GP Database is a rich source for data regarding people with T2D. In the Netherlands, T2D is mainly treated by GPs and is managed in a disease management programme by so called care groups.[31, 32] A care group is "an organisation in which care providers are associated who are responsible for the delivery of chronic care to a specific patient population in which a bundled payment contract is used".[33] In this case, bundled payment is a pricing model for long-term disease management, and an evaluation of three years of bundled payments for diabetes care showed that this model resulted in better registration of several process indicators (e.g., HbA_{1c}, BMI, blood pressure, cholesterol, foot examinations and kidney function testing).[34] Consequently, the availability and frequency of these indicators keeps increasing in the PHARMO DIAMANT cohort and makes it possible to perform (pharmaco)epidemiological studies with more advanced statistical analyses. For example, multiple measurements per patient over time can be used to perform time-dependent analyses and to use mixed effects models for repeated measures. Mixed effects models allow missing time points and use available information from the patients with missing time points and similar patients to estimate the least square means (LSM) at each time point.[35]

However, it should be kept in mind that data collected through GPs are not primarily collected for research purposes, but originate as documentation of the administration of GPs. The data include information items considered important or obligatory (e.g., weight), but lack data items not (yet) considered important for decision making in current daily practice (e.g., level of education). Because of this, we could not correct for all potential relevant confounders. For example, in the GP Database information regarding BMI is only

consistently available for people with diabetes since the introduction of the care groups in 2010. For patients not suffering from diabetes, BMI information is limited available.

To study the association between diabetes and/or blood glucose lowering drugs and cancer, the PHARMO DIAMANT cohort was linked to the NCR. The NCR comprises detailed information on newly diagnosed cancer patients in the Netherlands. The linkage between PHARMO DIAMANT and NCR created unique opportunities to perform (pharmaco) epidemiological studies with detailed information on diabetes, use of blood glucose lowering drugs and cancer.

Methodology

Over the past decades, it has become clear that the association between diabetes and/or blood glucose lowering drugs and cancer is prone to bias and that many methodological challenges are present. Confounding by indication, selection bias, the definition of the latency period, competing risks, exposure-trend bias, and the classification of cancer are a couple of examples which were encountered during the conduct of this thesis.

Confounding by indication is one of the most important threats to the validity of pharmaco-epidemiologic research. It occurs when the indication or reason for which the drug is prescribed, is also associated with the outcome. Because of the rather strict Dutch diabetes guideline for GPs, the newer blood glucose lowering drugs are prescribed to people who do not properly react to common, inexpensive standard therapy. Therefore, comparable patients not treated or treated with another drug and the same a priori baseline risk profile most likely do not exist in daily practice. In addition, the choice of a particular drug can also depend on the potential association with adverse events. All these choices, incidental or structural, impact the assessment of the effectiveness and the risk of adverse events of drugs using data obtained from daily practice. The influences of these known and unknown reasons and choices made by doctors are eliminated by random assignment of participants to treatment and control groups in RCTs, but apparent in observational studies. Consequently, effectiveness of new(er) blood glucose lowering drugs may be underestimated and the risk of adverse effects overestimated. Awareness of the channelling phenomenon is crucial to prevent that the benefit-risk-ratio of older, generally cheaper drugs, is overestimated. Controlling for confounding by indication in pharmaco-epidemiological studies is especially a challenge in the Netherlands, because the lack of heterogeneity in blood glucose lowering treatment. In Chapter 4, propensity score matching was performed to reduce the effect of confounding by indication.

Furthermore, a challenge in the clarification of the association between diabetes and/or blood glucose lowering drugs and cancer is that the effects typically first become manifest several years after drug initiation.[36] To allow for a sufficient latency period and to minimise reverse causality, we excluded studies with less than one year of follow-up (Chapter 6) and

INDEX

performed sensitivity analyses by considering a 1-year lag period (Chapter 8). In the studies included in our systematic review (Chapter 6) as well as our study regarding the association between diabetes and site-specific colorectal cancer (Chapter 8) the follow-up time ranged from 1.0 to 6.6 years, but was still rather short. A major concern in studies on cancer is the lack of knowledge regarding the (variability in) latency of carcinogenic drug effects.

In **Chapter 9** we studied the influence of a matching design compared to a non-matching design and determined whether different approaches for censoring or exclusion of people with incident diabetes during follow-up influenced the results. However, matching or not matching and different censoring definitions did not alter the results regarding the association between diabetes and breast, prostate or colorectal cancer. Furthermore, patients who died or were diagnosed with another cancer were no longer at risk of developing the cancer of interest. These events were competing risks which either hinders the observation of the event of interest or modifies the chance that this event occurs.[37] Therefore, competing-risk regression models were used in our study to meet the independent censoring assumption, which would be violated when using a Kaplan-Meier method.

An overall concern of (pharmaco)epidemiological studies is exposure-trend bias, which deserves some further attention. In Chapter 2, we observed an increase in the prevalence of diabetes in the period 1999-2014. During that same period the Dutch society aged and the proportion of people with obesity in the Netherlands increased. Both ageing and obesity are risk factors for cancer. The importance of these risk factors together with their trend parallel to the trend of the prevalence of diabetes introduces a complex epidemiological problem. The introduction of new blood glucose lowering drugs may coincide with an increased number of people with cancer due to the increasing trend of ageing and/or obesity. This phenomenon in pharmacoepidemiology is referred to as confounding of exposure trends,[38] in ultimo resulting in an increased risk of cancer incorrectly attributed to the newly introduced blood glucose lowering drugs.

Another overall consideration is the classification of cancer. Initially, studies evaluating the association between diabetes and cancer often considered cancer as one disease. Later it was acknowledged that cancer should not be seen as one disease and different types of cancer should be studied. Since then, it was found that associations with diabetes even differ between different sites of colorectal cancer.[39] This finding was also observed in our study regarding sex- and site-specific differences in colorectal cancer risk among people with T2D. In our study regarding T2D and/or insulin (analogue) treatment and specific breast cancer characteristics, we found different associations of T2D on different breast cancer characteristics. It has been hypothesised that not all cancers are susceptible to the potential growth-promoting effects of T2D, but that specific subtypes of cancers will respond to the metabolic abnormalities found in T2D.[40]

Considering all these (potential) biases and methodological challenges, pharmaco-epidemiological reasoning is pivotal to draw correct conclusions from studies in a real-world setting.

Future perspectives

Based on the research presented in this thesis, the following recommendations can be made.

Implication for practice

Results of this thesis showed a stronger association of glycaemic burden with micro- and macrovascular complications than a single point measurement of HbA_{1c}. It may be worthwhile to explore the additive predictive value of glycaemic burden compared to a single point measurement of HbA_{1c} for risk of complications. If so, the performance of current clinical prediction models to calculate patients' risk of micro- and/or macrovascular complications could be improved including patients' glycaemic burden. Furthermore, the PHARMO DIAMANT cohort can be used to develop other prediction models, such as predicting the optimal monitoring frequency or treatment.

Ongoing monitoring

The increasing number of people with diabetes and the still unclear safety and effectiveness of new and old blood glucose lowering treatments, stresses the need for more pharmacoepidemiological studies in this field. The PHARMO DIAMANT cohort showed to be a unique cohort providing the opportunity to gain real-life insights into the treatment and outcomes among people with diabetes in daily practice. In addition, the PHARMO DIAMANT cohort makes it possible to provide quick and up to date-information regarding the prevalence and treatment patterns of diabetes in the Netherlands, which is of importance for policy makers and regulators.

Expansion of data

Different blood glucose lowering drugs may act differently on carcinogenesis and also carcinogenesis differs per cancer type, subsite and subtype. The linkage between the PHARMO DIAMANT cohort and the NCR was used to perform these studies in the current thesis. Many subgroup analyses are needed to disentangle the complex association between diabetes and cancer. Even with the large number of patients, power of studies was sometimes still not sufficient. Combining the data from the PHARMO DIAMANT cohort with similar data from other countries, would create possibilities to study unanswered questions. However, due to the General Data Protection Regulation (GDPR), patient-based data required for (pharmaco)epidemiological research cannot be pooled into a single database. Here, it is not an option to bring data to the research but to standardise data in the different countries and disseminate statistical analyses scripts. Results from these scripts; aggregated

INDEX

results, can be shared and pooled. An option to ease this is the use of a common data model (CDM). A CDM was used in this thesis when studying the T2D treatment patterns in five different countries. One of the best known examples is the observational medical outcomes partnership (OMOP). OMOP is a public-private partnership aimed at the development of a CDM and vocabulary for observational healthcare databases. Once a database is mapped to the OMOP CDM, a set of tools is available to perform quality assessments and various analytic methods. The standardised databases make it possible to perform international collaborations. However, a big challenge of mapping regional coding systems to international standards is that some regional codes cannot be mapped, which will result in information loss.[41] Great understanding of the data that goes into the database and understanding of the database itself is pivotal. An OMOP approach will not always be applicable and each study (with or without combining data from different countries) deserves its own approach.

Conclusion

The prevalence of diabetes is increasing much faster than we could have expected based on changes in population demographics and is expected to increase further in the coming decades in the Netherlands and worldwide. The alleged association between blood glucose lowering drugs and cancer may prevent people with diabetes from being treated optimally. However, we were not able to find compelling evidence that diabetes and/or blood glucose lowering drugs are associated with an increased risk of cancer. Based on the current status of the field and the research presented in this thesis, more unbiased observational research is needed to disentangle the complex association between diabetes and/or blood glucose lowering drugs and cancer. In conclusion, we could not substantiate that drugs used to treat diabetes increase the risk of developing cancer.

INDEX

References

1. Bao C, Yang X, Xu W, Luo H, Xu Z, Su C, et al. Diabetes mellitus and incidence and mortality of kidney cancer: a meta-analysis. **J Diabetes Complications**. 2013; 27: 357-364.
2. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, et al. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. **Eur J Cancer**. 2011; 47: 1928-1937.
3. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. **Cancer Epidemiol Biomarkers Prev**. 2006; 15: 2056-2062.
4. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. **J Natl Cancer Inst**. 2005; 97: 1679-1687.
5. Wang P, Kang D, Cao W, Wang Y, Liu Z. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. **Diabetes Metab Res Rev**. 2012; 28: 109-122.
6. Zhang ZH, Su PY, Hao JH, Sun YH. The role of preexisting diabetes mellitus on incidence and mortality of endometrial cancer: a meta-analysis of prospective cohort studies. **Int J Gynecol Cancer**. 2013; 23: 294-303.
7. Zhu Z, Zhang X, Shen Z, Zhong S, Wang X, Lu Y, et al. Diabetes mellitus and risk of bladder cancer: a meta-analysis of cohort studies. **PLoS One**. 2013; 8: e56662.
8. van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, Vreugdenhil G, Pruijt JF, Coebergh JW, et al. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. **Eur J Cancer**. 2010; 46: 395-404.
9. Herings RMC, Pedersen L. Pharmacy-based Medical Record Linkage Systems. In: Strom B, Kimmel S, Hennessy S, (eds). Pharmacy-based Medical Record Linkage Systems. 5 ed: John Wiley & Sons, Ltd.; 2012. 270-286.
10. Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief (PALGA). Available from: http://www.palga.nl/. Accessed January 22, 2019.
11. Dutch Hospital Data (DHD). Available from: https://www.dhd.nl. Accessed January 22, 2019.
12. (IKNL) IKN. Available from: https://www.iknl.nl/. Accessed January 22, 2017.
13. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Percentage volwassenen met overgewicht en obesitas van 1981-2012. Available from: https://www.volksgezondheidenzorg.info/onderwerp/overgewicht/cijfers-context/trends#node-trend-overgewicht-bij-volwassenen. Accessed March 1, 2016.
14. Rutten GEHM, De Grauw WJC, Nijpels G, Goudswaard AN, Uitewaal PJM, Van der Does FEE, et al. NHG-Standaard Diabetes mellitus type 2 (Tweede herziening). **Huisarts Wet**. 2006; 49: 137-152.
15. Verduijn MM, Janssen PGH. NHG-Standpunt DPP-4-remmers en GLP-1-agonisten. 2010.

INDEX

16. Suissa S. Metformin to Treat Cancer: Misstep in Translational Research from Observational Studies. **Epidemiology**. 2017; 28: 455-458.
17. But A, De Bruin ML, Bazelier MT, Hjellvik V, Andersen M, Auvinen A, et al. Cancer risk among insulin users: comparing analogues with human insulin in the CARING five-country cohort study. **Diabetologia**. 2017; 60: 1691-1703.
18. Wang H, Liu Y, Tian Q, Yang J, Lu R, Zhan S, et al. Incretin-based therapies and risk of pancreatic cancer in patients with type 2 diabetes: a meta-analysis of randomised controlled trials. **Diabetes Obes Metab**. 2017.
19. Tseng CH. Sitagliptin and oral cancer risk in type 2 diabetes patients. **Oncotarget**. 2017; 8: 96753-96760.
20. Abrahami D, Douros A, Yin H, Yu OH, Faillie JL, Montastruc F, et al. Incretin based drugs and risk of cholangiocarcinoma among patients with type 2 diabetes: population based cohort study. **BMJ**. 2018; 363: k4880.
21. Abrahami D, Yin H, Yu OHY, Pollak MN, Azoulay L. Incretin-based Drugs and the Incidence of Colorectal Cancer in Patients with Type 2 Diabetes. **Epidemiology**. 2018; 29: 246-253.
22. Lai SW, Lin CL, Liao KF. Association Between Pancreatic Cancer and Dipeptidyl Peptidase-4 Inhibitors Use in a Case-Control Study. **Mayo Clin Proc**. 2018; 93: 1874-1876.
23. Montvida O, Green JB, Atherton J, Paul SK. Treatment with incretins does not increase the risk of pancreatic diseases compared to older anti-hyperglycaemic drugs, when added to metformin: real world evidence in people with Type 2 diabetes. **Diabet Med**. 2018.
24. Lee DY, Yu JH, Park S, Han K, Kim NH, Yoo HJ, et al. The influence of diabetes and antidiabetic medications on the risk of pancreatic cancer: a nationwide population-based study in Korea. **Sci Rep**. 2018; 8: 9719.
25. Bronsveld HK. Unravelling the link between diabetes, insulin treatment and breast cancer: Utrecht University; 2017.
26. de Kort S, Masclee AAM, Sanduleanu S, Weijenberg MP, van Herk-Sukel MPP, Oldenhof NJJ, et al. Higher risk of colorectal cancer in patients with newly diagnosed diabetes mellitus before the age of colorectal cancer screening initiation. **Sci Rep**. 2017; 7: 46527.
27. de Kort S, Simons CC, van den Brandt PA, Goldbohm RA, Arts IC, de Bruine AP, et al. Diabetes mellitus type 2 and subsite-specific colorectal cancer risk in men and women: results from the Netherlands Cohort Study on diet and cancer. **Eur J Gastroenterol Hepatol**. 2016; 28: 896-903.
28. Diaz-Algorri Y, Lozada ME, Lopez SM, Bertran-Rodriguez CE, Gonzalez-Hernandez CM, Gonzalez D, et al. Type 2 diabetes mellitus and colorectal neoplasia risk in Hispanics: a case-control study. **J Diabetes Complications**. 2015; 29: 502-507.
29. Sikdar KC, Walsh SJ, Roche M, Jiang Y, Syrowatka A, Collins KD. Diabetes and sex-specific colorectal cancer risks in Newfoundland and Labrador: a population-based retrospective cohort study. **Can J Public Health**. 2013; 104: e101-107.

INDEX

30. Woo H, Lee J, Lee J, Park JW, Park S, Kim J, et al. Diabetes Mellitus and Site-specific Colorectal Cancer Risk in Korea: A Case-control Study. **J Prev Med Public Health**. 2016; 49: 45-52.
31. Vektis. Factsheet Diabetes. Available from: https://www.zorgprismapubliek.nl/producten/patientgroepen/diabetes/. Accessed July 27, 2018.
32. Zonneveld N, Vat LE, Vlek H, Minkman MM. The development of integrated diabetes care in the Netherlands: a multiplayer self-assessment analysis. **BMC Health Serv Res**. 2017; 17: 219.
33. Struijs JN, van Til JT, Baan CA. Experimenteren met de keten-dbc diabetes. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu (RIVM), 2009.
34. Struijs JN, de Jong-van Til JT, Lemmens LC, Drewes HW, de Bruin SR, Baan CA. Three years of bundled payment for diabetes care in the Netherlands. Bilthoven: National Institute for Public Health and the Environment (RIVM) Ministry of Health, Welfare and Sport, 2012.
35. Ashbeck EL, Bell ML. Single time point comparisons in longitudinal randomized controlled trials: power and bias in the presence of missing data. **BMC Med Res Methodol**. 2016; 16: 43.
36. Pottegard A, Friis S, Sturmer T, Hallas J, Bahmanyar S. Considerations for Pharmacoepidemiological Studies of Drug-Cancer Associations. **Basic Clin Pharmacol Toxicol**. 2018; 122: 451-459.
37. Noordzij M, Leffondre K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? **Nephrol Dial Transplant**. 2013; 28: 2670-2677.
38. Greenland S. Confounding and exposure trends in case-crossover and case-time-control designs. **Epidemiology**. 1996; 7: 231-239.
39. Zanders MM, van Steenbergen LN, Haak HR, Rutten HJ, Pruijt JF, Poortmans PM, et al. Diminishing differences in treatment between patients with colorectal cancer with and without diabetes: a population-based study. **Diabet Med**. 2013; 30: 1181-1188.
40. Gallagher EJ, LeRoith D. Obesity and Diabetes: The Increased Risk of Cancer and Cancer-Related Mortality. **Physiol Rev**. 2015; 95: 727-748.
41. van Wijngaarden RPT. (2017) Applying the OMOP Common Data model to Dutch healthcare data: a case study.

INDEX